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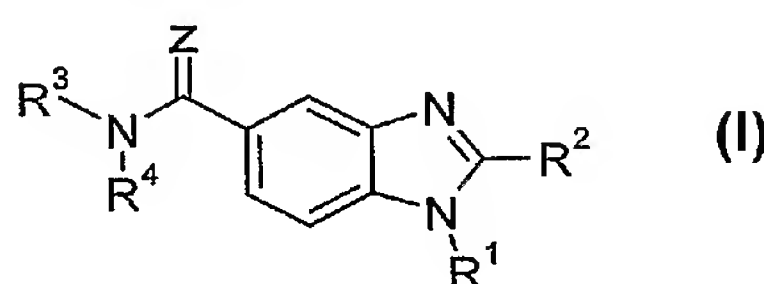
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(54) Title: BENZIMIDAZOLE DERIVATIVES, COMPOSITIONS CONTAINING THEM, PREPARATION THEREOF AND
USES THEREOF



(57) Abstract: Compounds of formula (I) or pharmaceutically acceptable salts thereof: wherein R₁, R₂, R₃, R₄ and Z are as defined in the specification as well as salts and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the management of pain.

**BENZIMIDAZOLE DERIVATIVES, COMPOSITIONS CONTAINING THEM,
PREPARATION THEREOF AND USES THEREOF**

BACKGROUND OF THE INVENTION

5 **1. Field of the invention**

The invention is related to therapeutic compounds which are CB₁ receptor ligands, pharmaceutical compositions containing these compounds, manufacturing processes thereof and uses thereof, and more particularly to compounds that are CB₁ receptor agonists. More particularly, the present invention is related to compounds that may be effective in treating
10 pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and cardiovascular disorders.

2. Discussion of Relevant Technology

Pain management has been an important field of study for many years. It has been well known that cannabinoid receptor (e.g., CB₁ receptor, CB₂ receptor) ligands including
15 agonists, antagonists and inverse agonists produce relief of pain in a variety of animal models by interacting with CB₁ and/or CB₂ receptors. Generally, CB₁ receptors are located predominately in the central nervous system, whereas CB₂ receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

20 While CB₁ receptor agonists, such as Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and anadamide, are useful in anti-nociception models in animals, they tend to exert undesired CNS side-effects, e.g., psychoactive side effects, the abuse potential, drug dependence and tolerance, etc. These undesired side effects are known to be mediated by the CB₁ receptors located in CNS. There are lines of evidence, however, suggesting that CB₁ agonists acting at
25 peripheral sites or with limited CNS exposure can manage pain in humans or animals with much improved overall in vivo profile.

Therefore, there is a need for new CB₁ receptor ligands such as agonists, antagonists or inverse agonists that are useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects.

30 **DISCLOSURE OF THE INVENTION**

The present invention provides CB₁ receptor ligands which are useful in treating pain and other related symptoms or diseases.

Definitions

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is
5 incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures. Optionally, a name of a compound may be generated using a chemical naming program: ACD/ChemSketch, Version 5.09/September 2001, Advanced Chemistry Development, Inc., Toronto, Canada.

"CB₁/CB₂ receptors" means CB₁ and/or CB₂ receptors.

10 The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms, and having 0 to n multivalent heteroatoms selected from O, S, N and P, wherein m and n are 0 or positive integers, and n>m. For example, "C₁₋₆" would refer to a chemical group having 1 to 6 carbon atoms, and having 0 to 6 multivalent heteroatoms selected from O, S, N and P.

15 The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

The term "hydrocarbon radical" or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.

20 The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms. Unless otherwise specified, "alkyl" general includes both saturated alkyl and unsaturated alkyl.

The term "alkylene" used alone or as suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serves to links two structures together.

25 The term "alkenyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 2 up to about 12 carbon atoms.

30 The term "alkynyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms.

The term "cycloalkyl," used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms.

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The term "cycloalkenyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

The term "cycloalkynyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon triple bond and comprising about 7 up to about 12 carbon atoms.

The term "aryl" used alone or as suffix or prefix, refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms, wherein the radical is located on a carbon of the aromatic ring.

The term "non-aromatic group" or "non-aromatic" used alone, as suffix or as prefix, refers to a chemical group or radical that does not containing a ring having aromatic character (*e.g.*, $4n + 2$ delocalized electrons).

The term "arylene" used alone or as suffix or prefix, refers to a divalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms, which serves to links two structures together.

The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The term "heteroalkyl" used alone or as a suffix or prefix, refers to a radical formed as a result of replacing one or more carbon atom of an alkyl with one or more heteroatoms selected from N, O, P and S.

The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-containing structure or molecule has an aromatic character (*e.g.*, $4n + 2$ delocalized electrons).

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The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocyclo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

5 The term "heterocyclyl" used alone or as a suffix or prefix, refers a monovalent radical derived from a heterocycle by removing one hydrogen from a carbon of a ring of the heterocycle.

The term "heterocyclylene" used alone or as a suffix or prefix, refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom, which serves to links two structures together.

10 The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character, wherein the radical of the heterocyclyl is located on a carbon of an aromatic ring of the heterocyclyl.

The term "heterocylcoalkyl" used alone or as a suffix or prefix, refers to a heterocyclyl that does not have aromatic character.

15 The term "heteroarylene" used alone or as a suffix or prefix, refers to a heterocyclylene having aromatic character.

The term "heterocycloalkylene" used alone or as a suffix or prefix, refers to a heterocyclylene that does not have aromatic character.

20 The term "six-membered" used as prefix refers to a group having a ring that contains six ring atoms.

The term "five-membered" used as prefix refers to a group having a ring that contains five ring atoms.

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

25 Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl.

30 A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

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The term "substituted" used as a prefix refers to a structure, molecule or group, wherein one or more hydrogens are replaced with one or more C₁₋₁₂hydrocarbon groups, or one or more chemical groups containing one or more heteroatoms selected from N, O, S, F, Cl, Br, I, and P. Exemplary chemical groups containing one or more heteroatoms include
5 heterocyclyl, -NO₂, -OR, -Cl, -Br, -I, -F, -CF₃, -C(=O)R, -C(=O)OH, -NH₂, -SH, -NHR, -NR₂, -SR, -SO₃H, -SO₂R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR₂, -NRC(=O)R, oxo (=O), imino (=NR), thio (=S), and oximino (=N-OR), wherein each "R" is a C₁₋₁₂hydrocarbyl. For example, substituted phenyl may refer to nitrophenyl, pyridylphenyl, methoxyphenyl, chlorophenyl, aminophenyl, etc., wherein the nitro, pyridyl, methoxy, chloro, and amino
10 groups may replace any suitable hydrogen on the phenyl ring.

The term "substituted" used as a suffix of a first structure, molecule or group, followed by one or more names of chemical groups refers to a second structure, molecule or group, which is a result of replacing one or more hydrogens of the first structure, molecule or group with the one or more named chemical groups. For example, a "phenyl substituted by
15 nitro" refers to nitrophenyl.

The term "optionally substituted" refers to both groups, structures, or molecules that are substituted and those that are not substituted.

Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine,
20 pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4-oxadiazole.
25

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene,
30

indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

5 In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

10 Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydro-pyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranal, thiopyranal, 2,3-dihydropyranal, tetrahydropyranal,
15 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl,
20 thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, quinolinyl,
25 tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizinyl, isoindolyl, indazolyl, purinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl,
30 phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrolizidinyl, and quinolizidinyl.

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In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and
5 7-oxabicyclo[2.2.1]heptyl.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula -O-R, wherein -R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

10 The term "aryloxy" used alone or as suffix or prefix, refers to radicals of the general formula -O-Ar, wherein -Ar is an aryl.

The term "heteroaryloxy" used alone or as suffix or prefix, refers to radicals of the general formula -O-Ar', wherein -Ar' is a heteroaryl.

15 The term "amine" or "amino" used alone or as a suffix or prefix, refers to radicals of the general formula -NRR', wherein R and R' are independently selected from hydrogen or a hydrocarbon radical.

"Acyl" used alone, as a prefix or suffix, means -C(=O)-R, wherein -R is an optionally substituted hydrocarbyl, hydrogen, amino or alkoxy. Acyl groups include, for example, acetyl, propionyl, benzoyl, phenyl acetyl, carboethoxy, and dimethylcarbamoyl.

20 Halogen includes fluorine, chlorine, bromine and iodine.

"Halogenated," used as a prefix of a group, means one or more hydrogens on the group is replaced with one or more halogens.

"RT" or "rt" means room temperature.

25 A first ring group being "fused" with a second ring group means the first ring and the second ring share at least two atoms therebetween.

"Link," "linked," or "linking," unless otherwise specified, means covalently linked or bonded.

30 When a first group, structure, or atom is "directly connected" to a second group, structure or atom, at least one atom of the first group, structure or atom forms a chemical bond with at least one atom of the second group, structure or atom.

"Saturated carbon" means a carbon atom in a structure, molecule or group wherein all the bonds connected to this carbon atom are single bond. In other words, there is no double or

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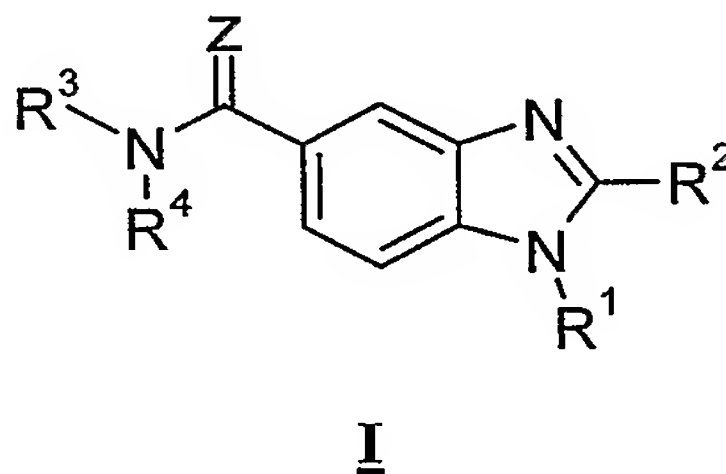
triple bonds connected to this carbon atom and this carbon atom generally adopts an sp^3 atomic orbital hybridization.

"Unsaturated carbon" means a carbon atom in a structure, molecule or group wherein at least one bond connected to this carbon atom is not a single bond. In other words, there is at least one double or triple bond connected to this carbon atom and this carbon atom generally adopts a sp or sp^2 atomic orbital hybridization.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be construed accordingly. The term "therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

Summary of the Invention

This invention encompasses compounds in accord with formula I:



wherein

Z is selected from O= and S=;

R^1 is selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $R^5R^6N-C_{1-6}$ alkyl, R^5O-C_{1-6} alkyl, $R^5C(=O)N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2-C_{1-6}$ alkyl, $R^5CS(=O)_2N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NC(=O)N(-R^7)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2N(R^7)-C_{1-6}$ alkyl, C_{6-10} aryl- C_{1-6} alkyl, C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-6}$ alkyl, C_{1-10} hydrocarbylamino, R^5R^6N- , R^5O- , $R^5C(=O)N(-R^6)-$, $R^5R^6NS(=O)_2-$, $R^5CS(=O)_2N(-R^6)-$, $R^5R^6NC(=O)N(-R^7)-$, $R^5R^6NS(=O)_2N(R^7)-$, C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-8} cycloalkenyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- $C(=O)-$; wherein said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{6-10} aryl- C_{1-6} alkyl, C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-6}$ alkyl, C_{1-10} hydrocarbylamino,

C₆₋₁₀aryl, C₆₋₁₀aryl-C(=O)-, C₃₋₁₀cycloalkyl, C₄₋₈cycloalkenyl, C₃₋₆heterocyclyl or C₃₋₆heterocyclyl-C(=O)- used in defining R¹ is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and -NR⁵R⁶;

5 R² is selected from the group consisting of C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl, R⁵R⁶N-, C₃₋₅heteroaryl, C₆₋₁₀aryl and C₃₋₆heterocycloalkyl, wherein said C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl, C₃₋₅heteroaryl, C₆₋₁₀aryl or C₃₋₆heterocycloalkyl used in defining R² is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and -NR⁵R⁶;

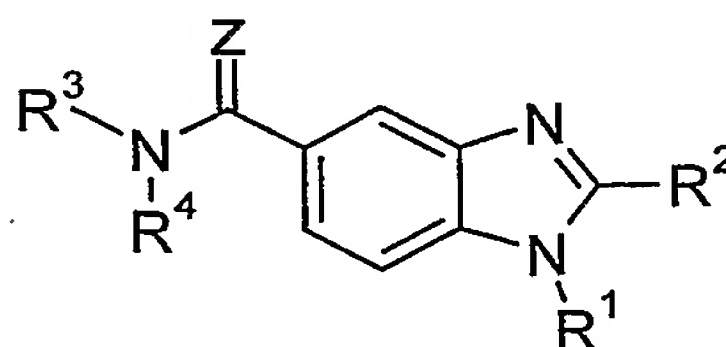
10 wherein R⁵, R⁶ and R⁷ are independently selected from -H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, and a divalent C₁₋₆group that together with another divalent R⁵, R⁶ or R⁷ form a portion of a ring; and

15 R³ and R⁴ are independently selected from -H, -OH, amino, R⁸ and -O-R⁸, wherein R⁸ is independently selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, and a divalent C₁₋₆group that together with another divalent R⁸ forms a portion of a ring, wherein R³ and R⁴ are not -H at the same time, and wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, or divalent C₁₋₆group in defining R⁸ is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, hydroxy, carboxy and -NR⁵R⁶; or R³ and R⁴ together with the nitrogen connected thereto form a portion of a 5- or 6-membered ring, wherein said ring is optionally substituted by one or more groupd selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, hydroxy, carboxy and -NR⁵R⁶.

25 The invention also encompasses stereoisomers, enantiomers, diastereomers, racemates or mixtures thereof, *in-vivo*-hydrolysable precursors and pharmaceutically-acceptable salts of compounds of formula I, solvated or unsolvated forms of compounds of formula I, pharmaceutical compositions and formulations containing them, methods of using them to treat diseases and conditions either alone or in combination with other therapeutically-active compounds or substances, processes and intermediates used to prepare them, uses of them as
30 medicaments, uses of them in the manufacture of medicaments and uses of them for diagnostic and analytic purposes.

Description of Preferred Embodiments

In one aspect, the invention provides a compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:

**I**

wherein

Z is selected from O= and S=;

R¹ is selected from C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, R⁵R⁶N-C₁₋₆alkyl, R⁵O-C₁₋₆alkyl, R⁵C(=O)N(-R⁶)-C₁₋₆alkyl, R⁵R⁶NS(=O)₂-C₁₋₆alkyl, R⁵CS(=O)₂N(-R⁶)-C₁₋₆alkyl, R⁵R⁶NC(=O)N(-R⁷)-C₁₋₆alkyl, R⁵R⁶NS(=O)₂N(R⁷)-C₁₋₆alkyl, C₆₋₁₀aryl-C₁₋₆alkyl, C₆₋₁₀aryl-C(=O)-C₁₋₆alkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocyclyl-C₁₋₆alkyl, C₃₋₆heterocyclyl-C(=O)-C₁₋₆alkyl, C₁₋₁₀hydrocarbylamino, R⁵R⁶N-, R⁵O-, R⁵C(=O)N(-R⁶)-, R⁵R⁶NS(=O)₂-, R⁵CS(=O)₂N(-R⁶)-, R⁵R⁶NC(=O)N(-R⁷)-, R⁵R⁶NS(=O)₂N(R⁷)-, C₆₋₁₀aryl, C₆₋₁₀aryl-C(=O)-, C₃₋₁₀cycloalkyl, C₄₋₈cycloalkenyl, C₃₋₆heterocyclyl and C₃₋₆heterocyclyl-C(=O)-; wherein said C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₆₋₁₀aryl-C₁₋₆alkyl, C₆₋₁₀aryl-C(=O)-C₁₋₆alkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocyclyl-C₁₋₆alkyl, C₃₋₆heterocyclyl-C(=O)-C₁₋₆alkyl, C₁₋₁₀hydrocarbylamino, C₆₋₁₀aryl, C₆₋₁₀aryl-C(=O)-, C₃₋₁₀cycloalkyl, C₄₋₈cycloalkenyl, C₃₋₆heterocyclyl or C₃₋₆heterocyclyl-C(=O)- used in defining R¹ is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and -NR⁵R⁶;

R² is selected from the group consisting of C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl, R⁵R⁶N-, C₃₋₅heteroaryl, C₆₋₁₀aryl and C₃₋₆heterocycloalkyl, wherein said C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl, C₃₋₅heteroaryl, C₆₋₁₀aryl or C₃₋₆heterocycloalkyl used in defining R² is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and -NR⁵R⁶;

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wherein R^5 , R^6 and R^7 are independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a divalent C_{1-6} group that together with another divalent R^5 , R^6 or R^7 form a portion of a ring; and

R^3 and R^4 are independently selected from $-H$, $-OH$, amino, R^8 and $-O-R^8$, wherein R^8 is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a divalent C_{1-6} group that together with another divalent R^8 forms a portion of a ring, wherein R^3 and R^4 are not $-H$ at the same time, and wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or divalent C_{1-6} group in defining R^8 is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, hydroxy, carboxy and $-NR^5R^6$; or R^3 and R^4 together with the nitrogen connected thereto form a portion of a 5- or 6-membered ring, wherein said ring is optionally substituted by one or more groupd selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, hydroxy, carboxy and $-NR^5R^6$.

Particularly, the compounds of the present invention are those of formula I, wherein Z is $O=$;

R^1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $R^5R^6N-C_{1-4}$ alkyl, R^5O-C_{1-4} alkyl, $R^5C(=O)N(-R^6)-C_{1-4}$ alkyl, phenyl- C_{1-4} alkyl, phenyl- $C(=O)-C_{1-4}$ alkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-4}$ alkyl, R^5R^6N- , R^5O- , $R^5R^6NS(=O)_2-$, C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-6} cycloalkenyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- $C(=O)-$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl- C_{1-4} alkyl, phenyl- $C(=O)-C_{1-4}$ alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-4}$ alkyl, C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-6} cycloalkenyl, C_{3-6} heterocyclyl or C_{3-6} heterocyclyl- $C(=O)-$ used in defining R^1 is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl, C_{3-5} heteroaryl, R^5R^6N- , phenyl and C_{3-6} heterocycloalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl, C_{3-5} heteroaryl, phenyl or C_{3-6} heterocycloalkyl used in defining R^2 is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and $-NR^5R^6$;

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R^3 and R^4 are independently selected from $-OH$, amino, C_{1-6} alkyl and C_{1-6} alkoxy, or R^3 and R^4 together with the nitrogen connected thereto form a portion of a 5- or 6-membered ring, wherein said ring is optionally substituted by a group selected from hydroxy, carboxy, methyl and ethyl; and

5 R^5 and R^6 are independently selected from $-H$, C_{1-6} alkyl and C_{2-6} alkenyl.

More particularly, the compounds of the present invention are those of formula I,

Z is $O=$;

R^1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, $R^5R^6N-C_{1-4}$ alkyl, R^5O-C_{1-4} alkyl, $R^5C(=O)N(-R^6)-C_{1-4}$ alkyl, phenyl- C_{1-4} alkyl, phenyl- $C(=O)-C_{1-4}$ alkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-4}$ alkyl, phenyl, C_{3-6} cycloalkyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- $C(=O)-$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, $R^5R^6N-C_{1-4}$ alkyl, R^5O-C_{1-4} alkyl, $R^5C(=O)N(-R^6)-C_{1-4}$ alkyl, phenyl- C_{1-4} alkyl, phenyl- $C(=O)-C_{1-4}$ alkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-4}$ alkyl, phenyl, C_{3-6} cycloalkyl, C_{3-6} heterocyclyl or C_{3-6} heterocyclyl- $C(=O)-$ used in defining R^1 is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, R^5R^6N- , C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl, C_{3-5} heteroaryl, and phenyl wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl, C_{3-5} heteroaryl, and phenyl used in defining R^2 is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;

R^5 and R^6 are independently selected from $-H$, C_{1-6} alkyl and C_{2-6} alkenyl; and

25 R^3 and R^4 are independently selected from $-OH$, amino, C_{1-6} alkyl and C_{1-6} alkoxy; or R^3 and R^4 together with the nitrogen connected thereto form a portion of a 5- or 6-membered ring wherein said ring is optionally substituted by a group selected from hydroxy, methoxy, ethoxy, methyl and ethyl.

Most particularly, the compounds of the present invention are those of formula I, wherein

Z is $O=$;

R^1 is selected from cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl, ethyl, propyl, adamantyl, adamantylmethyl, allyl, isopentyl, benzyl,

methoxyethyl, tetrahydropyranylmethyl, tetrahydrofuranylmethyl, cyclohexyloxy, cyclohexylamino, dimethylaminoethyl, 4-pyridylmethyl, 2-pyridylmethyl, 1-pyrrolylethyl, 1-morpholinoethyl, 4,4-difluorocyclohexylmethyl, cyclohexylmethyl, 2-pyrrolidylmethyl, N-methyl-2-pyrrolidylmethyl, 2-piperidylmethyl, N-methyl-2-piperidylmethyl, 3-thienylmethyl, (2-nitrothiophene-5-yl)-methyl, (1-methyl-1H-imidazole-2-yl)methyl, (5-(acetoxymethyl)-2-furyl)methyl, (2,3-dihydro-1H-isoindole-1-yl)methyl, and 5-(2-methylthiazolyl);

R^2 is selected from t-butyl, n-butyl, 2-methyl-2-butyl, cyclohexyl, cyclohexylmethyl, n-pentyl, isopentyl, trifluoromethyl, 1,1-difluoroethyl, N-piperidyl, dimethylamino, phenyl, pyridyl, tetrahydrofuranyl, tetrahydropyranyl, N-morpholinyl, and 2-methoxy-2-propyl; and

R^3 and R^4 are independently selected from methyl, ethyl, hydroxy, methoxy and ethoxy; or R^3 and R^4 together with the nitrogen connected thereto form a group selected from isoxazolidin-2-yl, 4-hydroxy-isoxazolidin-2-yl, 4-hydroxy-4-methyl-isoxazolidin-2-yl, N-morpholinyl.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I. It will further be understood that the present invention encompasses tautomers of the compounds of the formula I.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the formula I.

Within the scope of the invention are also salts of the compounds of the formula I.

Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to

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make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a
5 suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of formula I above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate,
10 methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB1 receptors. More particularly, the compounds of the invention exhibit selective activity as agonist of the CB1 receptors and are useful in therapy,
15 especially for relief of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive. Additionally, compounds of the present invention are useful in other disease states in which dysfunction of CB1 receptors is present or implicated. Furthermore, the compounds of the invention may be used to treat cancer,
20 multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and cardiovascular disorders.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral
25 agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of cannabinoid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

30 Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental illnesses, cough, lung oedema, various

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gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson's disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following myocardial infarction, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other
5 drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled
10 anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering
15 from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of formula I, or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula I,
20 or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be construed accordingly. The term "therapy" within the context of
25 the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for the
30 therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by

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any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracically, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be orally,
5 intravenously or intramuscularly.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

10 For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents,
15 flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and
20 compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized moulds and allowed to cool and solidify.

25 Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active
30 component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

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Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

5 Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other
10 suspending agents known to the pharmaceutical formulation art.

 Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

15 A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

 Within the scope of the invention is the use of any compound of formula I as defined
20 above for the manufacture of a medicament.

 Also within the scope of the invention is the use of any compound of formula I for the manufacture of a medicament for the therapy of pain.

 Additionally provided is the use of any compound according to Formula I for the manufacture of a medicament for the therapy of various pain conditions including, but not
25 limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

 A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I above, is administered to a patient in need of such therapy.

30 Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

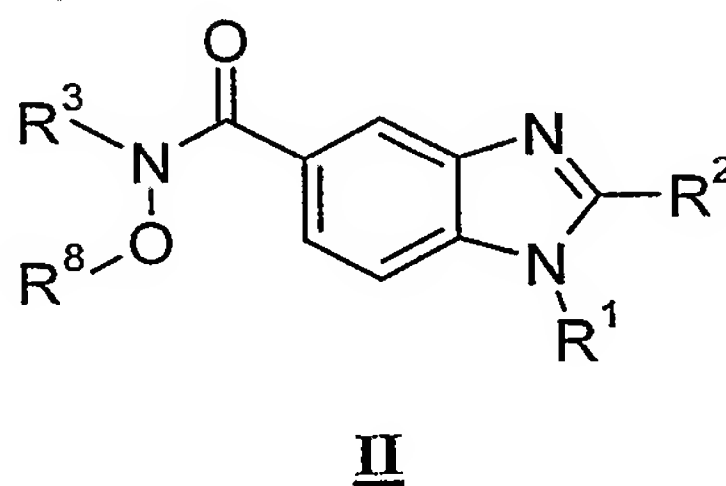
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Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

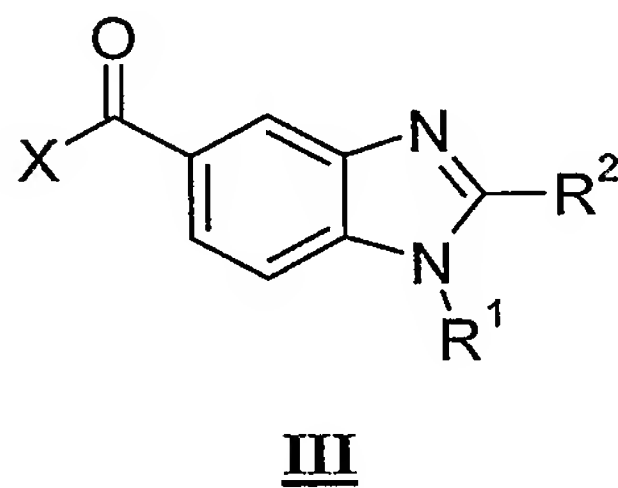
Further, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

In a further aspect, the present invention provides a method of preparing the compounds of the present invention.

In one embodiment, the invention provides a process for preparing a compound of formula II, comprising of the step of



reacting a compound of formula III,



with a compound of R^3NHOR^8 to form the compound of formula II, wherein

X is selected from Cl, Br, I and OH;

R^1 is selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $R^5R^6N-C_{1-6}$ alkyl, R^5O-C_{1-6} alkyl, $R^5C(=O)N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2-C_{1-6}$ alkyl, $R^5CS(=O)_2N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NC(=O)N(-R^7)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2N(R^7)-C_{1-6}$ alkyl, C_{6-10} aryl- C_{1-6} alkyl, C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-6}$ alkyl, C_{1-10} hydrocarbylamino, R^5R^6N- , R^5O- , $R^5C(=O)N(-R^6)-$, $R^5R^6NS(=O)_2-$, $R^5CS(=O)_2N(-R^6)-$, $R^5R^6NC(=O)N(-R^7)-$, $R^5R^6NS(=O)_2N(R^7)-$, C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-8} cycloalkenyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- $C(=O)-$; wherein said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{6-10} aryl- C_{1-6} alkyl,

C₆₋₁₀aryl-C(=O)-C₁₋₆alkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocyclyl-C₁₋₆alkyl, C₃₋₆heterocyclyl-C(=O)-C₁₋₆alkyl, C₁₋₁₀hydrocarbylamino, C₆₋₁₀aryl, C₆₋₁₀aryl-C(=O)-, C₃₋₈cycloalkyl, C₄₋₈cycloalkenyl, C₃₋₆heterocyclyl or C₃₋₆heterocyclyl-C(=O)- used in defining R¹ is optionally substituted by one or more groups
 5 selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and -NR⁵R⁶;

R² is selected from the group consisting of C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl, R⁵R⁶N-, C₃₋₅heteroaryl, C₆₋₁₀aryl and C₃₋₆heterocycloalkyl, wherein
 10 said C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl, C₃₋₅heteroaryl, C₆₋₁₀aryl or C₃₋₆heterocycloalkyl used in defining R² is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;

15 wherein R⁵, R⁶ and R⁷ are independently selected from -H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, and a divalent C₁₋₆group that together with another divalent R⁵, R⁶ or R⁷ forms a portion of a ring;

R³ is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, and a divalent C₁₋₆group that together with a divalent R⁸ forms a portion of a ring; and

20 R⁸ is selected from -H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, and a divalent C₁₋₆group that together with a divalent R³ forms a portion of a ring.

Particularly, the present invention provides a method of preparing a compound of formula II, wherein R¹ is selected from cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl, ethyl, propyl, adamantyl, adamantylmethyl, allyl, isopentyl, benzyl, methoxyethyl, tetrahydropyranylmethyl, tetrahydrofuranylmethyl, cyclohexyloxy, cyclohexylamino, dimethylaminoethyl, 4-pyridylmethyl, 2-pyridylmethyl, 1-pyrrolylethyl, 1-morpholinoethyl, 4,4-difluorocyclohexylmethyl, cyclohexylmethyl, 2-pyrrolidylmethyl, N-methyl-2-pyrrolidylmethyl, 2-piperidylmethyl, N-methyl-2-piperidylmethyl, 3-thienylmethyl, (2-nitrothiophene-5-yl)-methyl, (1-methyl-1H-imidazole-2-yl)methyl, (5-(acetoxymethyl)-2-furyl)methyl, (2,3-dihydro-1H-isoindole-1-yl)methyl, and
 30 5-(2-methylthiazolyl);

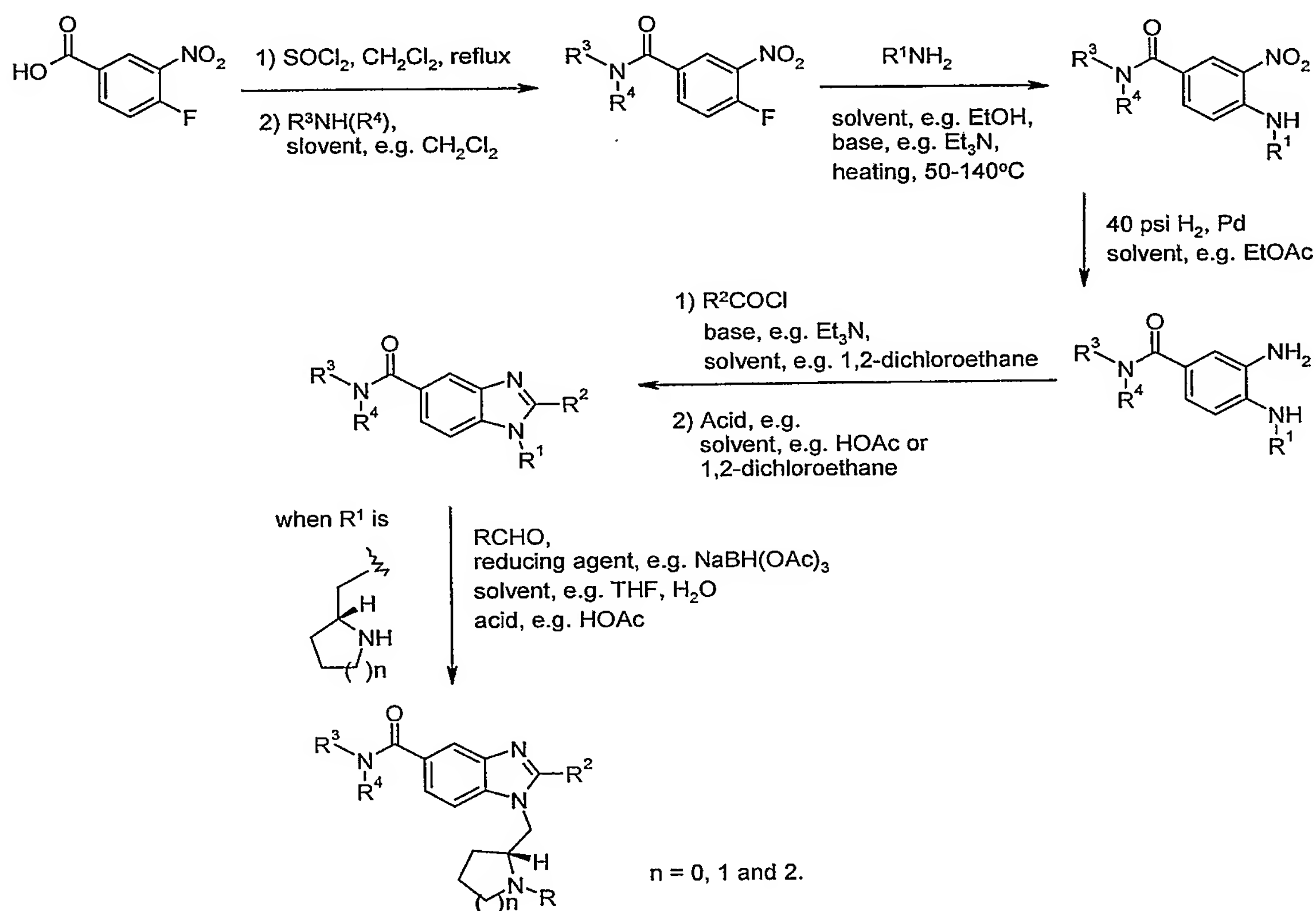
- 20 -

R^2 is selected from t-butyl, n-butyl, 2-methyl-2-butyl, cyclohexyl, cyclohexylmethyl, n-pentyl, isopentyl, trifluoromethyl, 1,1-difluoroethyl, N-piperidyl, dimethylamino, phenyl, pyridyl, tetrahydrofuranyl, tetrahydropyranyl, 2-methoxy-2-propyl, and N-morpholinyl; and

R^3 and R^4 are independently C_{1-6} alkyl.

5 Compounds of the present invention may be prepared according to the synthetic routes as depicted in Schemes 1-3 using one or more methods disclosed above.

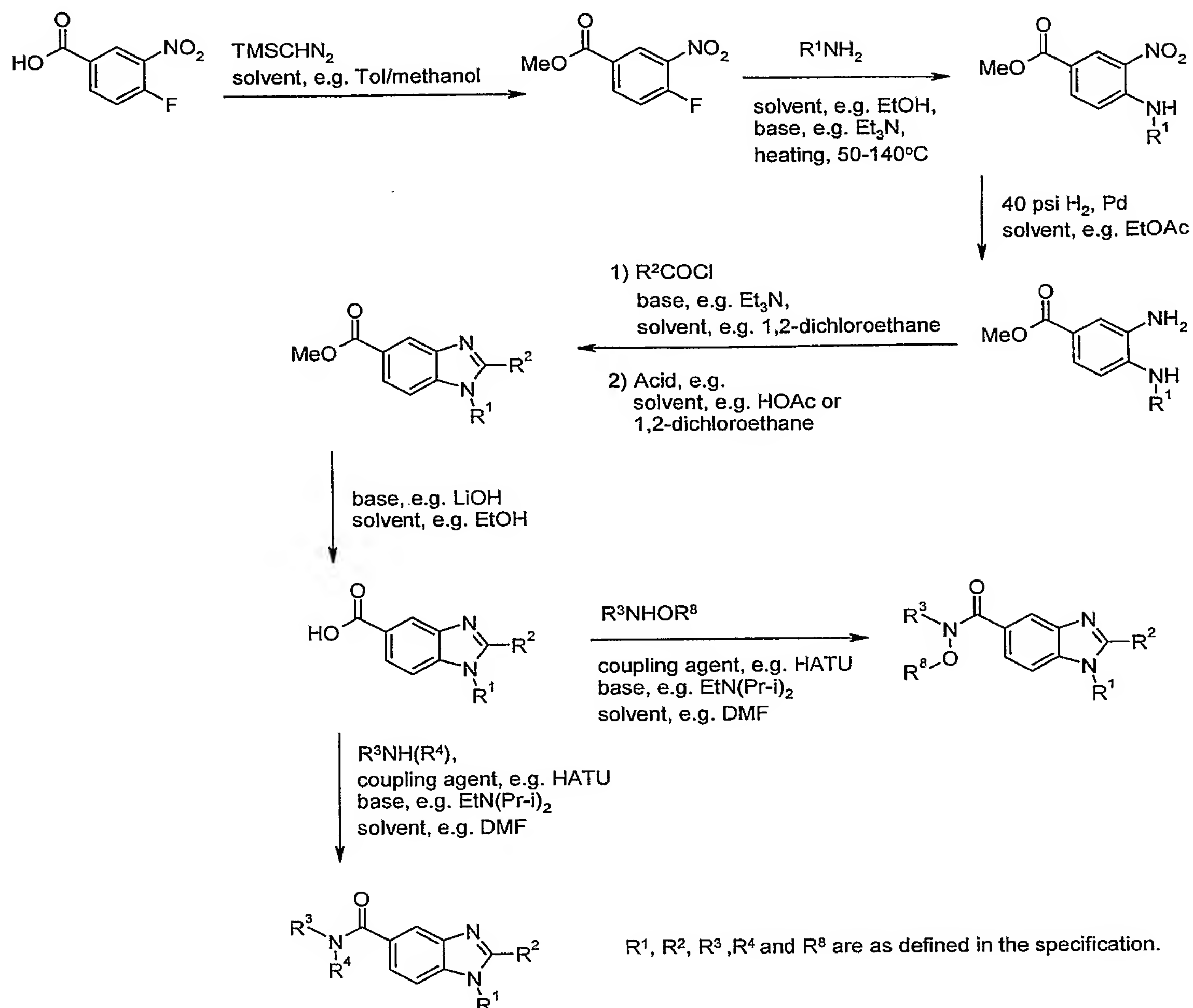
Scheme 1. (A synthetic route used for the synthesis of compounds including Examples 1 and 2)



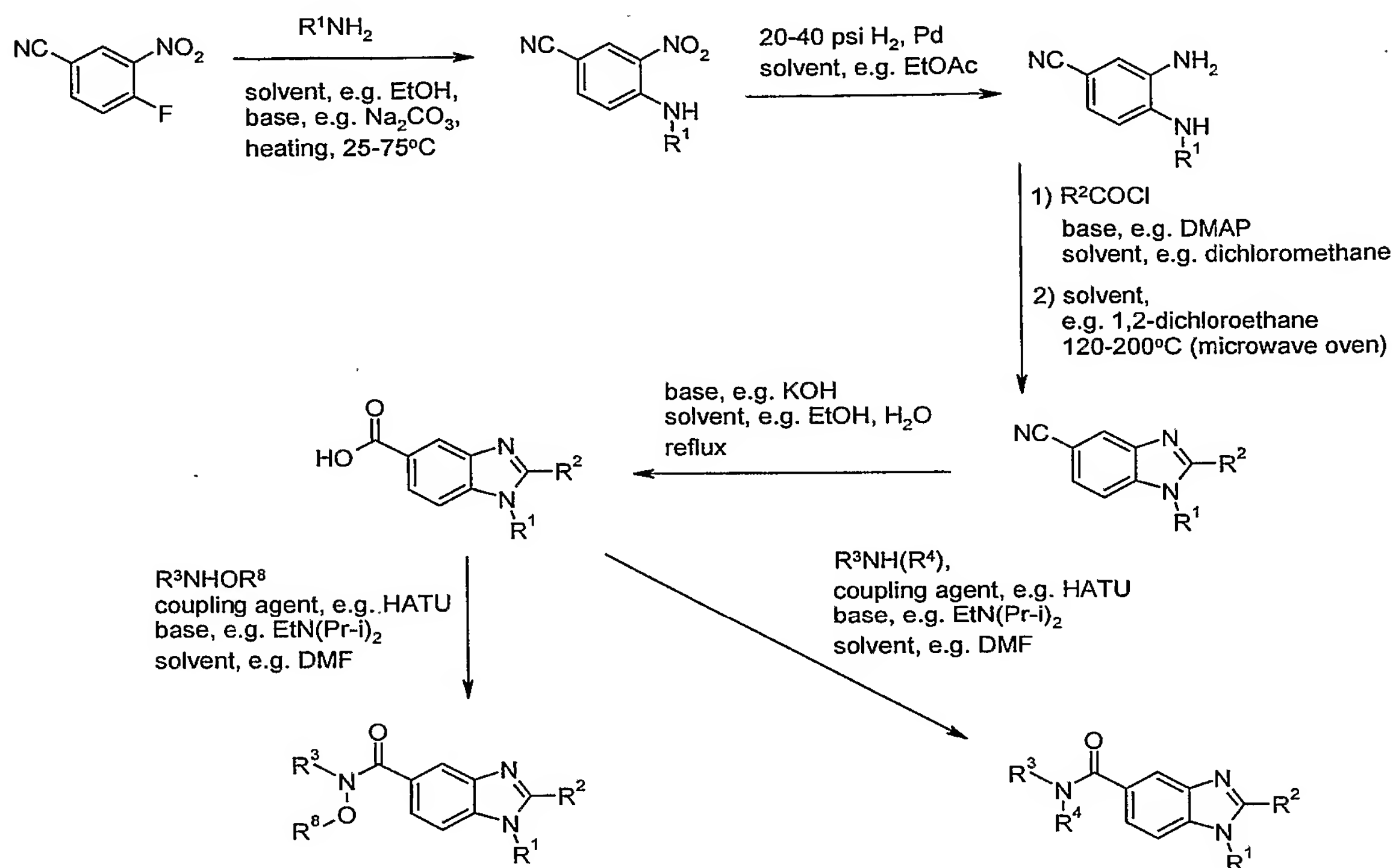
R^1 , R^2 , R^3 and R^4 are as defined in the specification. R is C_{1-6} alkyl.

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Scheme 2. (A synthetic route used for the synthesis of compounds including Examples 3 and 23)



Scheme 3. (A synthetic route used for the synthesis of compounds including Examples 4-22)



R^1 , R^2 , R^3 and R^8 are as defined in the specification.

Biological Evaluation

hCB₁ and hCB₂ receptor binding

- 5 Human CB₁ receptor from Receptor Biology (hCB₁) or human CB₂ receptor from BioSignal (hCB₂) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM MgCl₂, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed in 96-well plates. The IC₅₀ of the compounds of the
- 10 invention at hCB₁ and hCB₂ are evaluated from 10-point dose-response curves done with ³H-CP55,940 at 20000 to 25000 dpm per well (0.17-0.21 nM) in a final volume of 300 µl. The total and non-specific binding are determined in the absence and presence of 0.2 µM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the
- 15 Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM MgCl₂, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid.

hCB₁ and hCB₂ GTP γ S binding

Human CB₁ receptor from Receptor Biology (hCB₁) or human CB₂ receptor membranes (BioSignal) are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end
5 needle and diluted in the GTP γ S binding buffer (50 mM Hepes, 20 mM NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM MgCl₂, pH 7.4, 0.1% BSA). The EC₅₀ and E_{max} of the compounds of the invention are evaluated from 10-point dose-response curves done in 300 μ l with the appropriate amount of membrane protein and 100000-130000 dpm of GTP γ ³⁵S per well (0.11 – 0.14 nM). The basal and maximal stimulated binding is determined in absence and presence
10 of 1 μ M (hCB₂) or 10 μ M (hCB₁) Win 55,212-2 respectively. The membranes are pre-incubated for 5 minutes with 56.25 μ M (hCB₂) or 112.5 μ M (hCB₁) GDP prior to distribution in plates (15 μ M (hCB₂) or 30 μ M (hCB₁) GDP final). The plates are vortexed and incubated for 60 minutes at room temperature, filtered on Unifilters GF/B (presoaked in water) with the Tomtec or Packard harvester using 3 ml of wash buffer (50 mM Tris, 5 mM MgCl₂, 50 mM
15 NaCl, pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 μ l/well of MS-20 scintillation liquid. Antagonist reversal studies are done in the same way except that (a) an agonist dose-response curve is done in the presence of a constant concentration of antagonist, or (b) an antagonist dose-response curve is done in the presence of a constant concentration of agonist.

20 Based on the above assays, the dissociation constant (K_i) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$$K_i = IC_{50} / (1 + [rad] / K_d),$$

Wherein IC₅₀ is the concentration of the compound of the invention at which 50% displacement has been observed;

25 [rad] is a standard or reference radioactive ligand concentration at that moment; and
K_d is the dissociation constant of the radioactive ligand towards the particular receptor.

Using above-mentioned assays, the K_i towards human CB₁ receptors for most compounds of the invention is measured to be in the range of 36-5700 nM. The K_i towards
30 human CB₂ receptors for most compounds of the invention is measured to be in the range of about 1.6-36 nM.

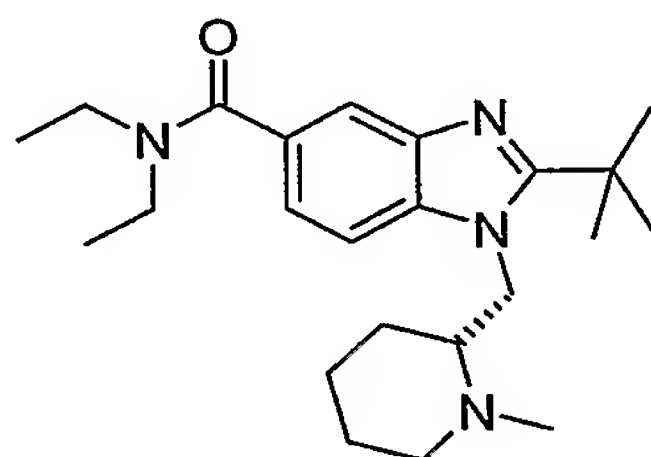
Using the above described assays, the IC₅₀ towards CB₁ receptor for most of the compounds of the present invention is generally in the range of 16.2 nM – 5655.7 nM.

EXAMPLES

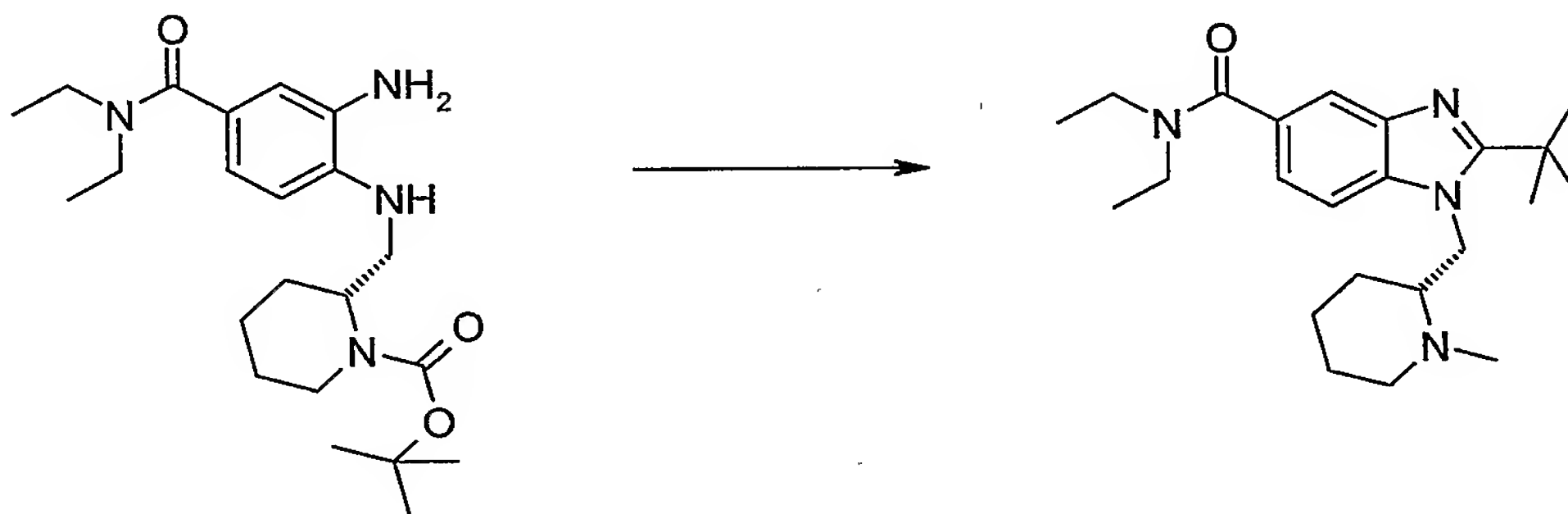
The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Example 1

2-*tert*-Butyl-*N,N*-diethyl-1-{[(2*R*)-1-methylpiperidin-2-yl]methyl}-1*H*-benzimidazole-5-carboxamide



Step A. 2-*tert*-Butyl-*N,N*-diethyl-1-{[(2*R*)-1-methylpiperidin-2-yl]methyl}-1*H*-benzimidazole-5-carboxamide

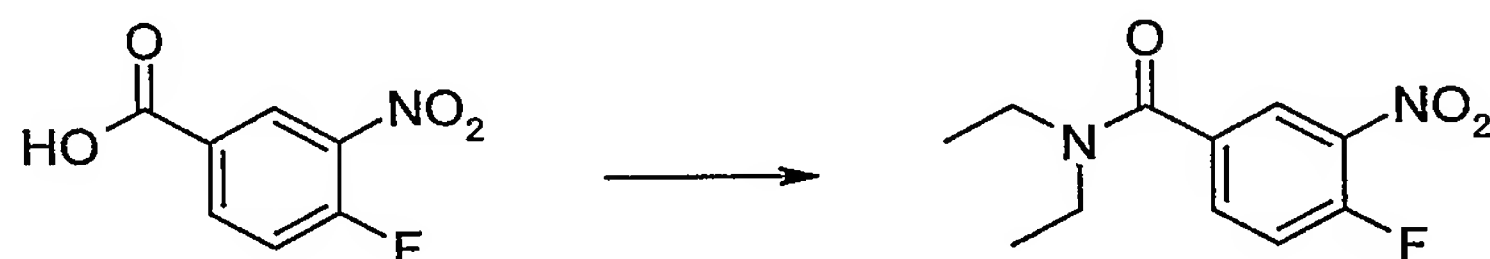


tert-Butyl (2*R*)-2-[(2-amino-4-[(diethylamino)carbonyl]phenyl)amino]methylpiperidine-1-carboxylate (75 mg, 0.185 mmol) (for preparation, see the following steps B, C, and D) was dissolved in 3 mL of DCE containing TEA (0.058 mL, 0.277 mmol). Trimethylacetyl chloride (0.025 mL, 0.204 mmol) was added drop wise and the solution was stirred at RT for 1h. Glacial acetic acid (1 mL) and a few drops of concentrated HCl were added and the solution was stirred at 75°C for 24h. The solvent was concentrated. The residue was dissolved in EtOAc and washed with 2M NaOH, brine and dried over anhydrous MgSO₄. The solvent was evaporated. The product was dissolved in 5 mL of THF containing a few drops of glacial AcOH. An excess of 37% HCHO/water (1 mL) was added followed by NaBH(OAc)₃ (78 mg, 0.370 mmol). The solution was stirred at rt for 30 min. The solution

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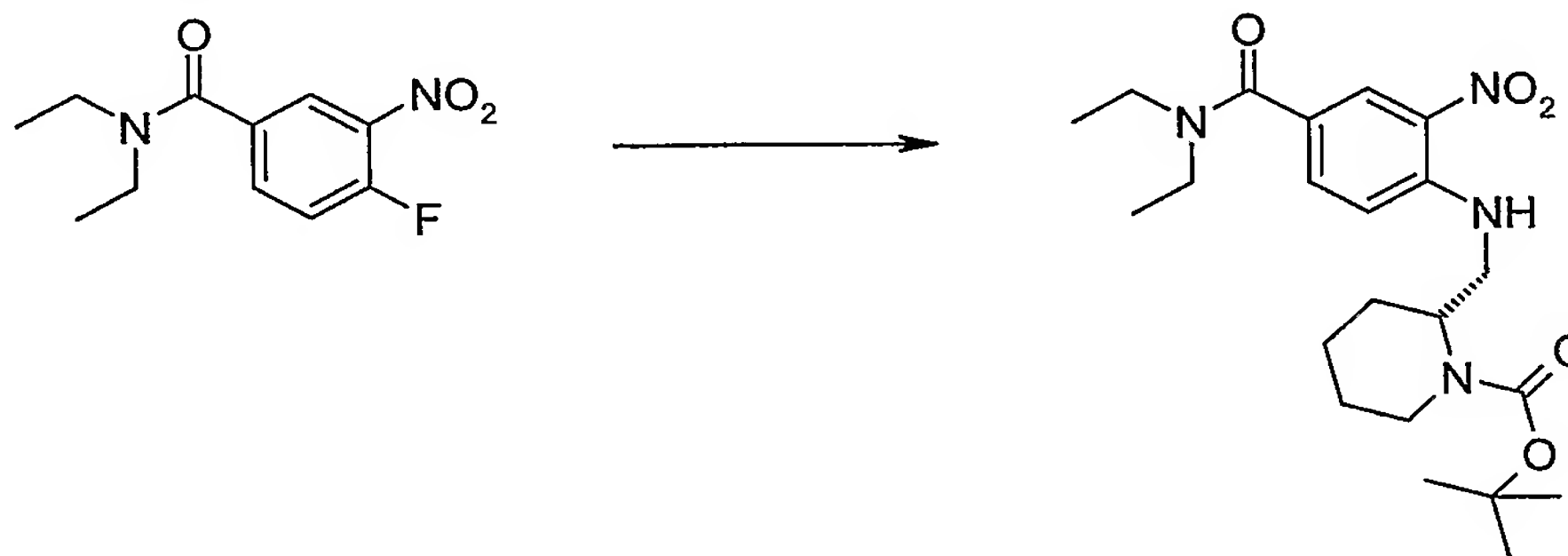
was diluted with EtOAc and washed with 2 M NaOH, brine and dried over anhydrous MgSO₄. The solvent was evaporated. The product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O and then lyophilized affording the desired title compound as the corresponding TFA salt. Yield: 42 mg (46%). ¹H NMR (400 MHz, CD₃OD) δ 1.12 (m, 3H), 1.25 (m, 3H), 1.36 (m, 2H), 1.65 (s, 9H), 1.79 (m, 2H), 1.87 (m, 1H), 3.15 (s, 3H), 3.31 (m, 3H), 3.57 (m, 3H), 4.01 (m, 1H), 4.85 (m, 1H), 5.18 (m, 1H), 7.50 (dd, J = 1.56, 8.59 Hz, 1H), 7.72 (d J = 0.98 Hz, 1H), 7.93 (d, J = 8.59 Hz, 1H); MS (ESI) (M+H)⁺ 385.3; Anal. Calcd for C₂₃H₃₆N₄O + 3.0 TFA: C, 47.94; H, 5.41; N, 7.71. Found: C, 48.06; H, 5.23; N, 7.85.

Step B. *N,N*-Diethyl-4-fluoro-3-nitro-benzamide



4-Fluoro-3-nitrobenzoic acid (5.0 g, 27.0 mmol) was refluxed in a 2:1 mixture of CH₂Cl₂/SOCl₂ (150 mL) overnight. The solvent was concentrated and the residue was dissolved in CH₂Cl₂ (50 mL). Another CH₂Cl₂ solution (50 mL) of diethylamine (3.35 mL, 32.4 mmol) and triethylamine (TEA) (7.5 mL, 54 mmol) was then added drop wise to the cold stirring solution (0°C) of the acid chloride. The solution was stirred at rt for 3h. The solution was then washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 1:1/hexanes:EtOAc on silica gel. Yield: 5.39 g (83%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.19 (b, 6 H), 3.24 (b, 2 H), 3.52 (b, 2 H), 7.33 (dd, J=10.45, 8.50 Hz, 1 H), 7.66 (m, 1 H), 8.09 (dd, J=7.03, 2.15 Hz, 1 H).

Step C. *tert*-butyl-(2*R*)-2-[(4-[(diethylamino)carbonyl]-2-nitrophenyl)amino)methyl]piperidine-1-carboxylate



N,N-Diethyl-4-fluoro-3-nitro-benzamide (210 mg, 0.874 mmol) and *tert*-butyl (2*R*)-2-(aminomethyl)piperidine-1-carboxylate (245 mg, 1.14 mmol) were stirred in 15 mL of EtOH

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containing TEA (0.185 mL, 1.31 mmol) at 75°C overnight. The solvent was concentrated.

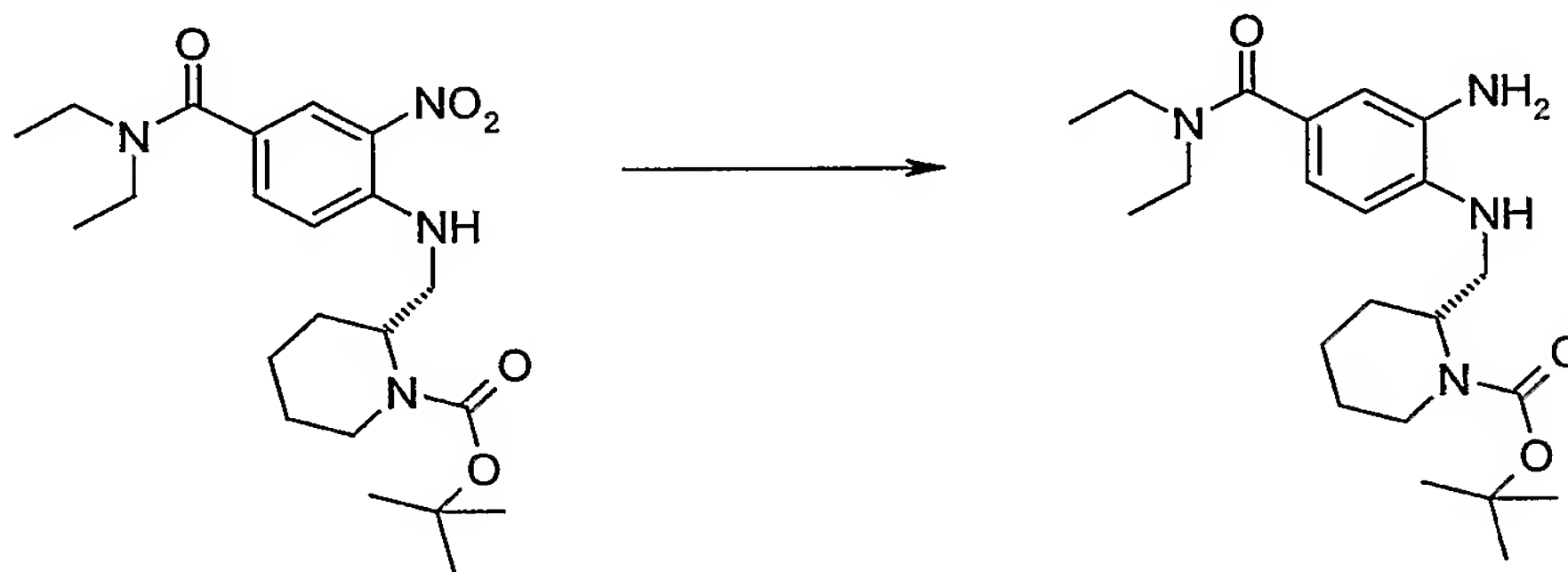
The residue was dissolved in EtOAc and washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified

by flash chromatography using 1:1 / hexanes:EtOAc as eluent on silica gel to produce the

desired title compound. Yield: 380 mg (99%). ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.22 (m, 6 H), 1.47 (s, 9 H), 1.55 (m, 1 H), 1.63 (m, 1 H), 1.71 (d, *J*=12.89 Hz, 4 H), 2.79 (m, 1 H), 3.36 (dd, *J*=12.89, 6.25 Hz, 1 H), 3.43 (m, 4 H), 3.61 (m, 1 H), 4.07 (m, 1 H), 4.62 (m, 1 H), 7.00 (m, *J*=8.79 Hz, 1 H), 7.57 (dd, *J*=8.79, 1.76 Hz, 1 H), 8.28 (d, *J*=1.76 Hz, 2 H).

Step D. *tert*-Butyl (2*R*)-2-[(2-amino-4-

[(diethylamino)carbonyl]phenyl]amino)methyl]piperidine-1-carboxylate



tert-Butyl-(2*R*)-2-[(4-[(diethylamino)carbonyl]-2-nitrophenyl]amino)methyl]piperidine-1-carboxylate (380 mg, 0.875 mmol) was dissolved in 35 mL of EtOAc containing a catalytic

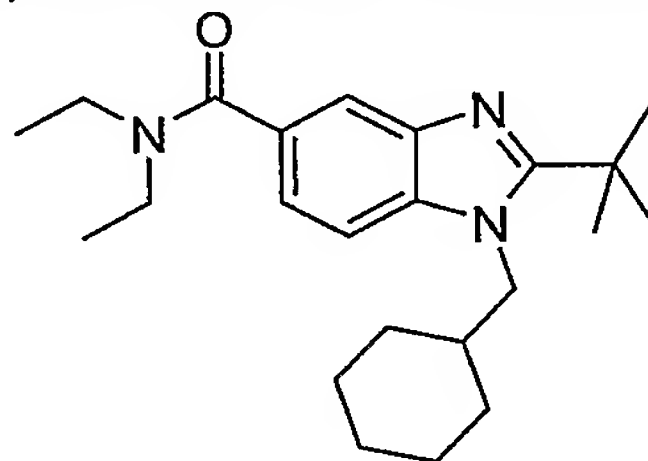
amount of 10% Pd/C. The solution was shaken in a Parr hydrogenation apparatus under H₂

atmosphere (40 psi) at RT overnight. The solution was filtered through Celite and the solvent was concentrated. The product was used directly for the next step without further

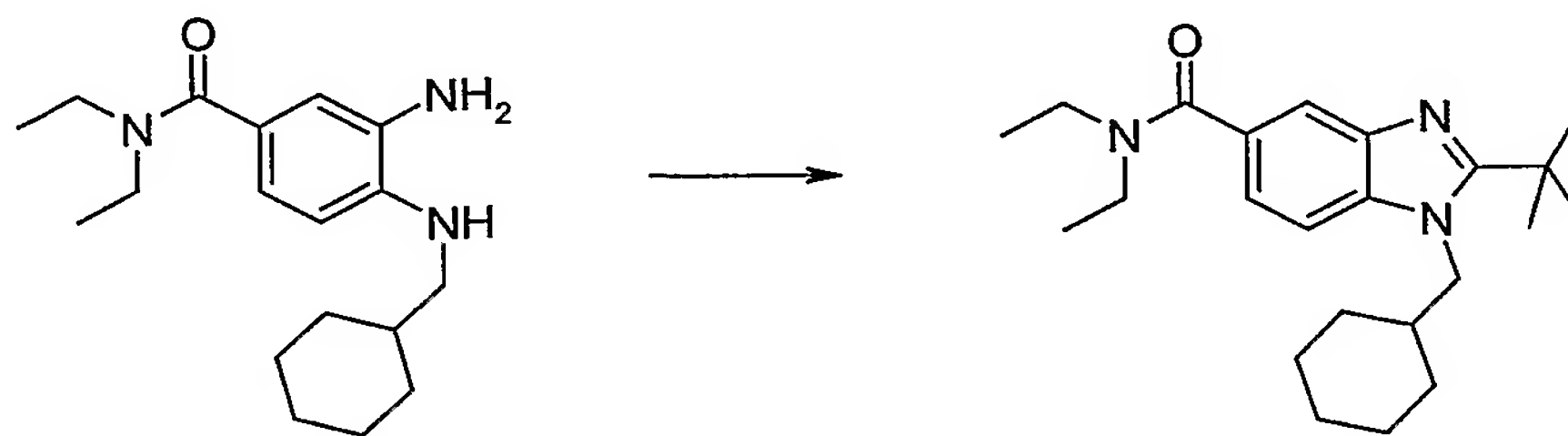
purification. Yield: 355 mg (99%). ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.17 (t, *J*=6.74 Hz, 6 H), 1.46 (s, 9 H), 1.55 (d, *J*=11.72 Hz, 1 H), 1.65 (d, *J*=10.35 Hz, 2 H), 1.73 (m, 2 H), 2.81 (t, *J*=12.50 Hz, 1 H), 3.09 (d, *J*=9.76 Hz, 1 H), 3.31 (m, 2 H), 3.42 (m, 4 H), 3.52 (m, 2 H), 4.02 (m, 1 H), 4.59 (m, 1 H), 6.58 (d, *J*=8.01 Hz, 1 H), 6.78 (d, *J*=1.56 Hz, 1 H), 6.86 (m, 1 H), 7.26 (s, 1 H).

Example 2

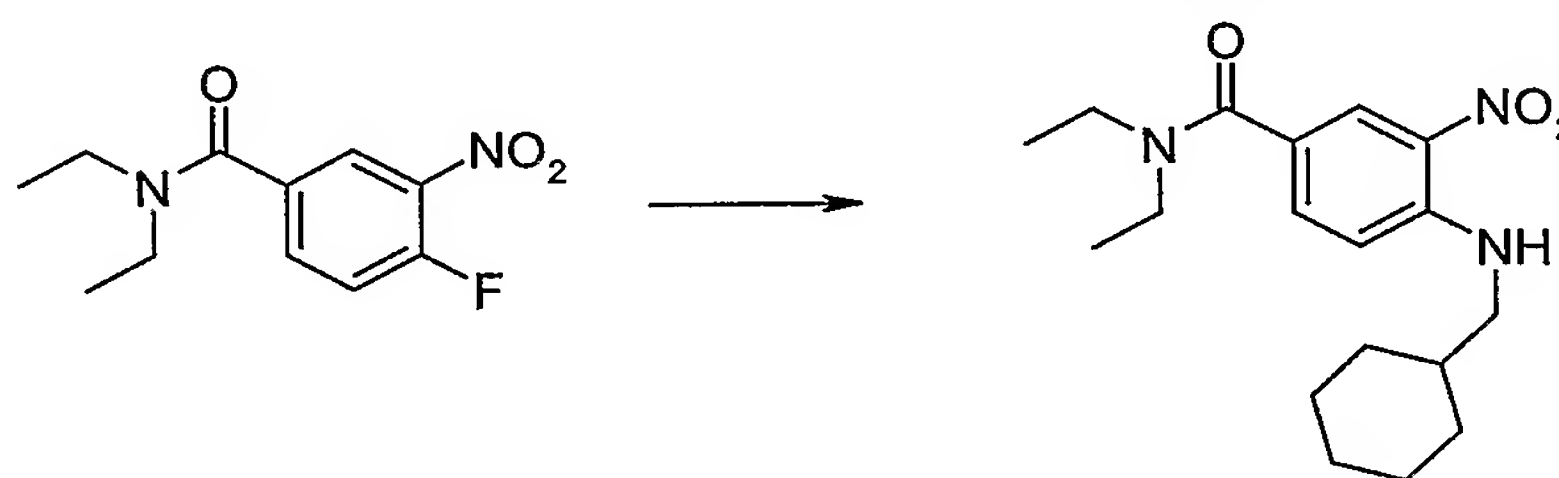
2-*tert*-Butyl-1-(cyclohexylmethyl)-*N,N*-diethyl-1*H*-benzimidazole-5-carboxamide



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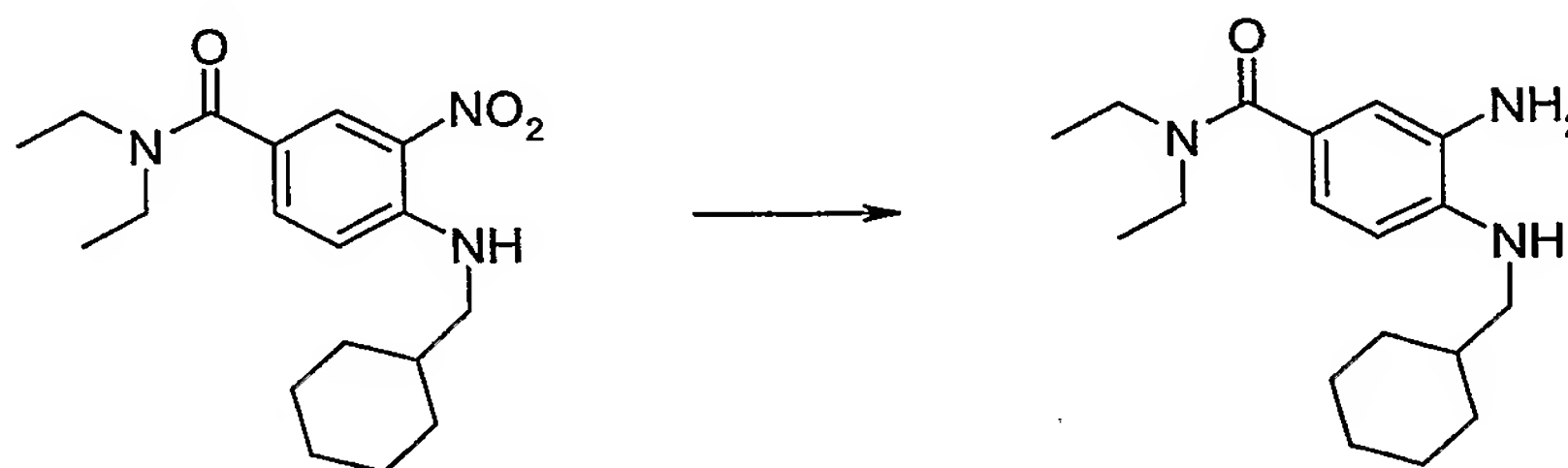
Step A. 2-tert-Butyl-1-(cyclohexylmethyl)-N,N-diethyl-1H-benzimidazole-5-carboxamide

3-Amino-4-[(cyclohexylmethyl)amino]-N,N-diethylbenzamide (124 mg, 0.409 mmol) (for preparation, see the following steps B and C) was dissolved in 3 mL of DCE containing TEA (0.085 mL, 0.614 mmol). Trimethylacetyl chloride (0.055 mL, 0.450 mmol) was added dropwise and the solution was stirred at RT for 1h. Glacial AcOH (1 mL) and a few drops of concentrated HCl were added and the solution was stirred at 75°C for 48h. The solvent was concentrated. The residue was dissolved in EtOAc and washed with 2M aqueous NaOH, brine and dried over anhydrous MgSO₄. The solvent was evaporated. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the desired title compound as the corresponding TFA salt. Yield: 64 mg (32%). ¹H NMR (400 MHz, CD₃OD) δ 1.12 (m, 3H), 1.23 (m, 7H), 1.67 (m, 14H), 1.75 (m, 1H), 2.11 (m, 1H), 3.28 (m, 2H), 3.56 (m, 2H), 4.48 (d, J = 7.42 Hz, 2H), 7.58 (dd, J = 1.46, 8.69 Hz, 1H), 7.73 (s, 1H), 7.99 (d, J = 8.79 Hz, 1H); MS (ESI) (M+H)⁺ 370.2; Anal. Calcd for C₂₃H₃₅N₃O + 2.1 TFA + 0.9 H₂O: C, 52.25; H, 6.27; N, 6.72. Found: C, 52.31; H, 6.24; N, 6.69.

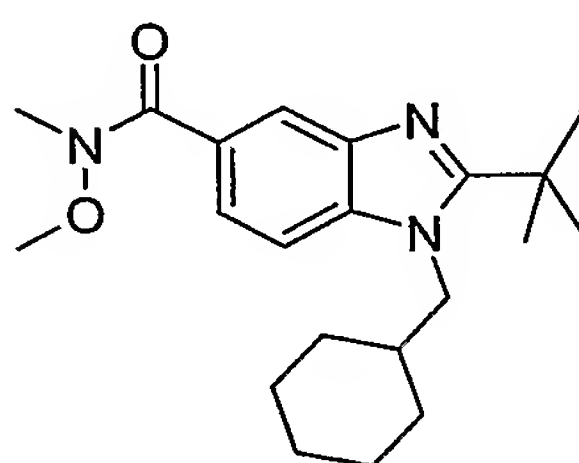
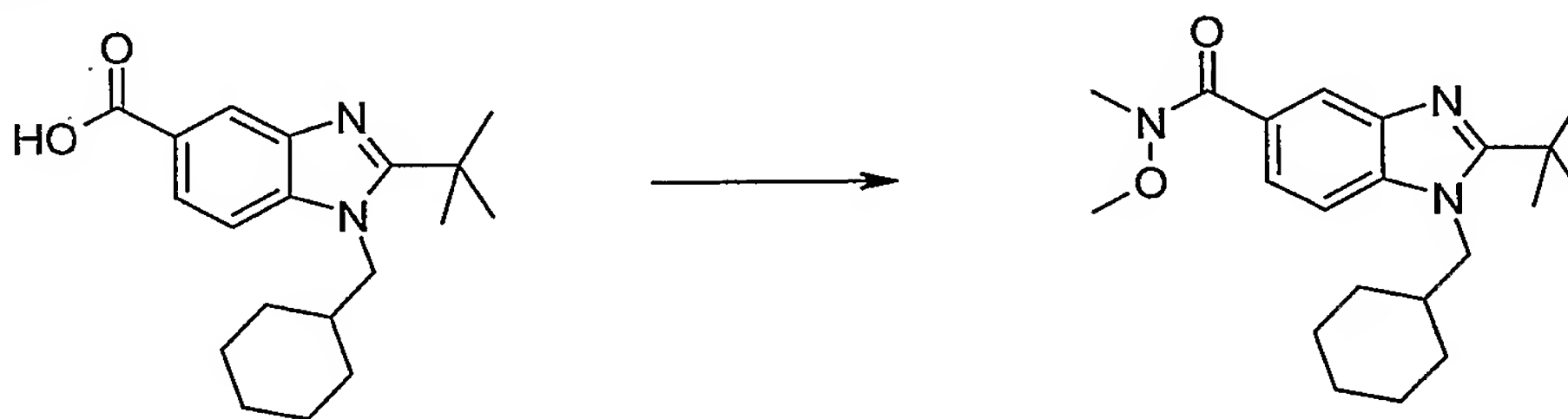
Step B. 4-[(Cyclohexylmethyl)amino]-N,N-diethyl-3-nitrobenzamide

Following the same procedure in Example 1, step C, using N,N-Diethyl-4-fluoro-3-nitrobenzamide (105 mg, 0.437 mmol) and cyclohexylmethylamine (0.090 mL, 0.656 mmol) in 5mL of EtOH containing TEA (0.135mL, 0.655mmol). The product was directly used for next step after regular washings. Yield: 144 mg (99%). ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.06 (m, 2 H) 1.22 (t, J=7.13 Hz, 7 H) 1.30 (m, 2 H) 1.71 (m, 2 H) 1.79 (m, 2 H) 1.86 (d, J=11.91 Hz, 2 H) 3.18 (m, 2 H) 3.45 (m, 4 H) 6.88 (d, J=8.79 Hz, 1 H) 7.55 (dd, J=8.88, 2.05 Hz, 1 H) 8.28 (d, J=1.95 Hz, 1 H) 8.31 (m, 1 H).

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Step C. 3-Amino-4-[(cyclohexylmethyl)amino]-*N,N*-diethylbenzamide

Following the same procedure in Example 1, step D, using 4-[(cyclohexylmethyl)amino]-*N,N*-diethyl-3-nitrobenzamide (140 mg, 0.420 mmol) and a catalytic amount of 10% Pd/C in 15 mL of EtOAc. The solution was filtered through Celite and used directly for next step. Yield: 125 mg (99%). MS (ESI) (M+H)⁺: 304.2.

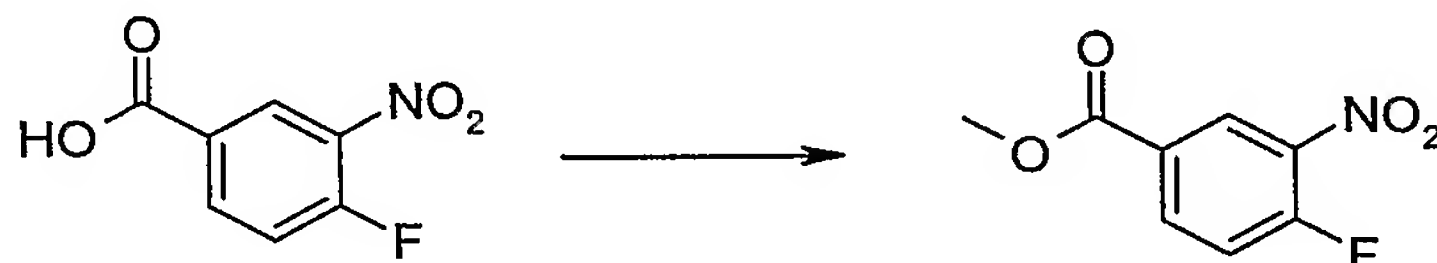
Example 3**2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methoxy-*N*-methyl-1*H*-benzimidazole-5-carboxamide****Step A. 2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methoxy-*N*-methyl-1*H*-benzimidazole-5-carboxamide**

2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazole-5-carboxylic acid (58 mg, 0.184 mmol) (for preparation, see the following Steps B to F), *N*,*O*-dimethylhydroxylamine hydrochloride (25 mg, 0.276 mmol) and HATU (77 mg, 0.202 mmol) were stirred in 2 mL of DMF containing DIPEA (0.080 mL, 0.460 mmol) at RT for 3h. The solvent was concentrated. The residue was dissolved in EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O on a C-18 column and then lyophilized affording the desired title compound as the corresponding TFA salt. Yield: 29 mg (33%). ¹H NMR (400

- 29 -

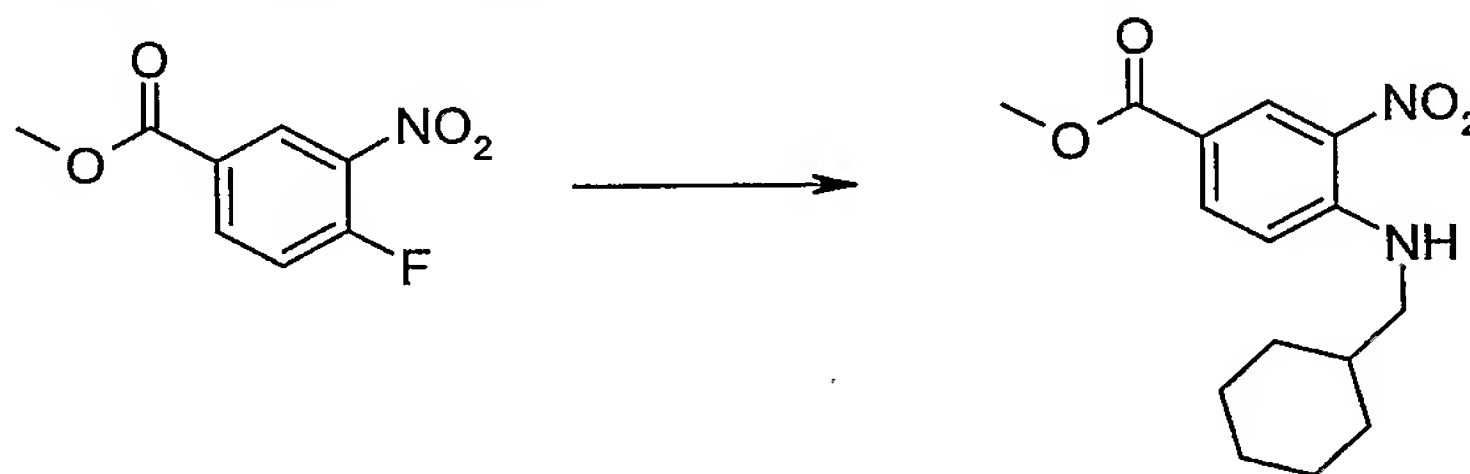
MHz, METHANOL-D₄) δ 1.23 (m, 5 H), 1.62 (s, 2 H), 1.65 (s, 9 H), 1.75 (m, 2 H), 2.11 (m, 1 H), 3.38 (s, 3 H), 3.56 (s, 3 H), 4.45 (d, $J=7.62$ Hz, 2 H), 7.82 (dd, $J=8.69, 1.46$ Hz, 1 H), 7.91 (m, 1 H), 8.03 (d, $J=0.78$ Hz, 1 H); MS (ESI) (M+H)⁺ 358.2; Anal. Calcd for C₂₁H₃₁N₃O₂ + 1.2 TFA + 0.3 H₂O: C, 56.24; H, 6.62; N, 8.41. Found: C, 56.28; H, 6.51; N, 8.48.

Step B. Methyl 4-fluoro-3-nitrobenzoate



4-Fluoro-3-nitrobenzoic acid (500 mg, 2.70 mmol) was dissolved in 20 mL of a 5:1 / toluene:MeOH mixture at 0°C under nitrogen. Trimethylsilyl diazomethane (2M in hexanes) (1.6 mL, 3.24 mmol) was added dropwise and the solution stirred at rt for 30 min. The solvent was concentrated. The product was purified by flash chromatography using 4:1 / hexanes:EtOAc as eluent on silica gel, to yield the desired title compound. Yield: 494 mg (92%). ¹H NMR (400 MHz, CHLOROFORM-D) δ 3.98 (s, 3 H), 7.39 (dd, $J=10.06, 8.49$ Hz, 1 H), 8.33 (ddd, $J=8.69, 4.20, 2.15$ Hz, 1 H), 8.75 (dd, $J=7.23, 2.15$ Hz, 1 H).

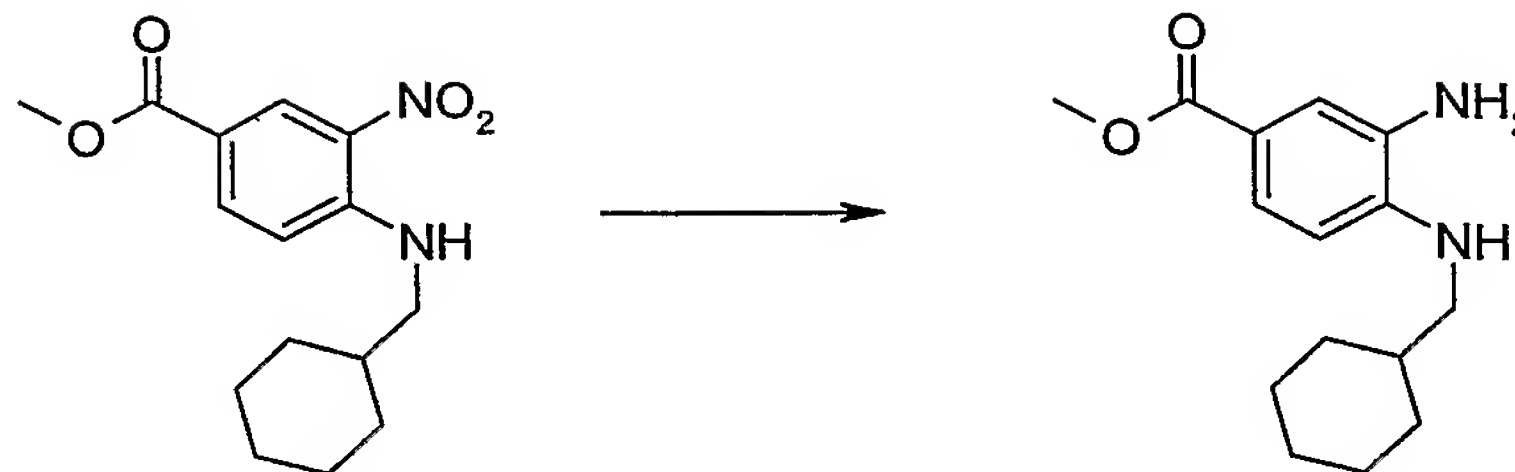
Step C. Methyl 4-[(cyclohexylmethyl)amino]-3-nitrobenzoate



Following the same procedure in Example 1, step C, using methyl 4-fluoro-3-nitrobenzoate (225 mg, 1.13 mmol) and cyclohexylmethylamine (0.175 mL, 1.36 mmol) in 5 mL of EtOH containing TEA (0.235 mL, 1.70 mmol). The product was directly used for next step after the regular washings. Yield: 329 mg (99%). ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.06 (m, 2H), 1.26 (m, 3H), 1.72 (m, 3H), 1.72 (m, 2H), 1.84 (m, 1H), 1.87 (m, 1H), 3.20 (dd, $J=6.64, 5.47$ Hz, 2H), 3.90 (s, 3H), 6.86 (d, $J=8.98$ Hz, 1H), 8.04 (ddd, $J=9.03, 2.10, 0.78$ Hz, 1H), 8.47 (s, 1H), 8.89 (d, $J=1.95$ Hz, 1H).

Step D. Methyl 3-amino-4-[(cyclohexylmethyl)amino]benzoate

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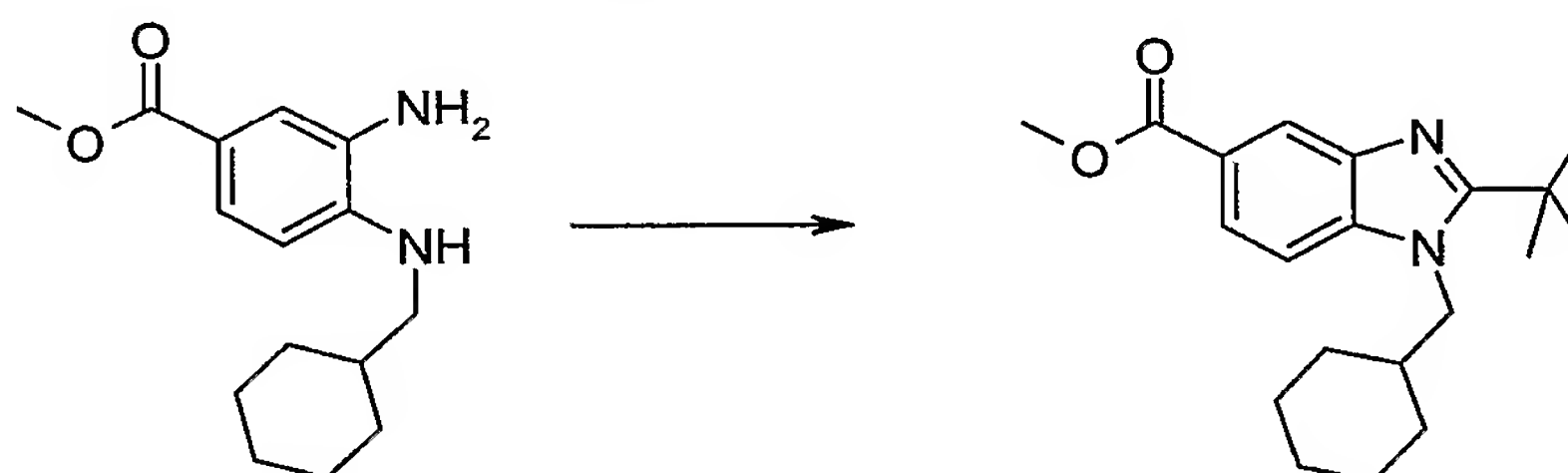


Following the same procedure in Example 1, step D, using methyl 4-

[(cyclohexylmethyl)amino]-3-nitrobenzoate (325 mg, 1.11 mmol) in 25 mL of EtOAc. The mixture was filtered through Celite and used directly in Step A. Yield: 285 mg (98%). MS

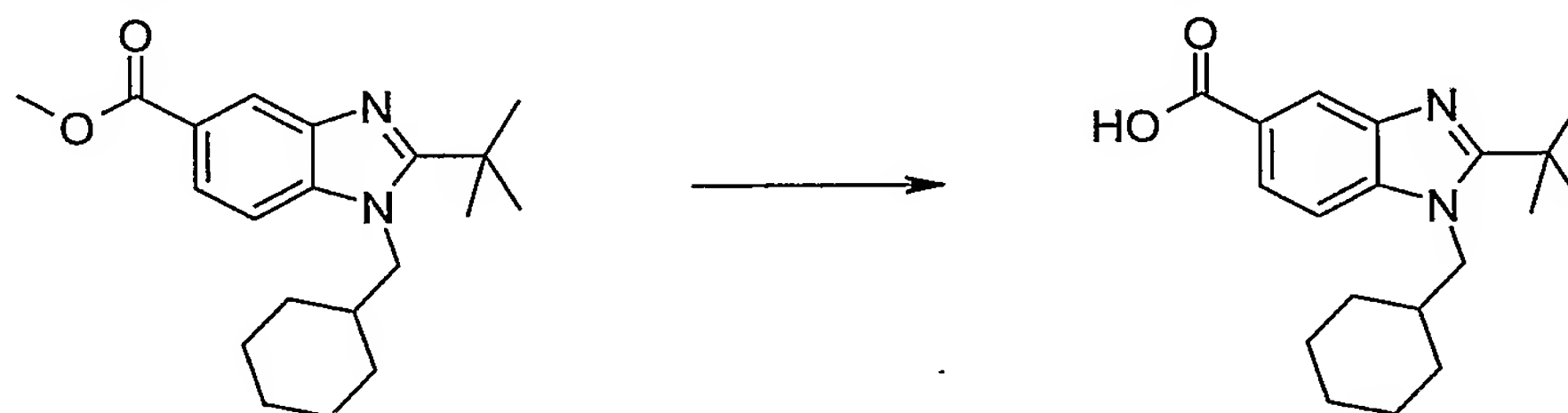
5 (ESI) (M+H)⁺: 263.0.

Step E. Methyl 2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazole-5-carboxylate



Methyl 3-amino-4-[(cyclohexylmethyl)amino]benzoate (285 mg, 1.09 mmol) was dissolved in 10 mL of DCM containing DMAP (33 mg, 0.272 mmol). Trimethylacetyl chloride (0.145 mL, 1.20 mmol) was added drop wise and the solution was stirred at RT for 2h. The solvent was concentrated. The residue was dissolved in 15 mL of glacial AcOH and stirred at 100°C for 24h. The solvent was concentrated. The residue was dissolved in EtOAc and the solution was washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by flash chromatography using 7:3 / hexanes:EtOAc as elute on silica gel. Yield: 170 mg (47%). ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.10 (m, 2H), 1.16 (m, 2H), 1.57 (s, 9H), 1.61 (m, 1H), 1.62 (m, 2H), 1.69 (m, 1H), 1.73 (m, 2H), 2.03 (m, 1H), 3.93 (s, 3H), 4.15 (d, J = 7.62 Hz, 2H), 7.34 (d, J = 8.59 Hz, 1H), 7.94 (dd, J = 8.59, 1.56 Hz, 1H), 8.47 (d, J = 0.98 Hz, 1H).

Step F. 2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazole-5-carboxylic acid

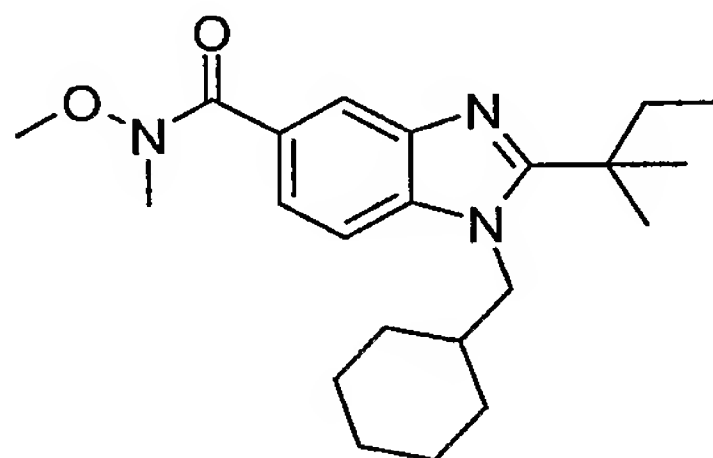


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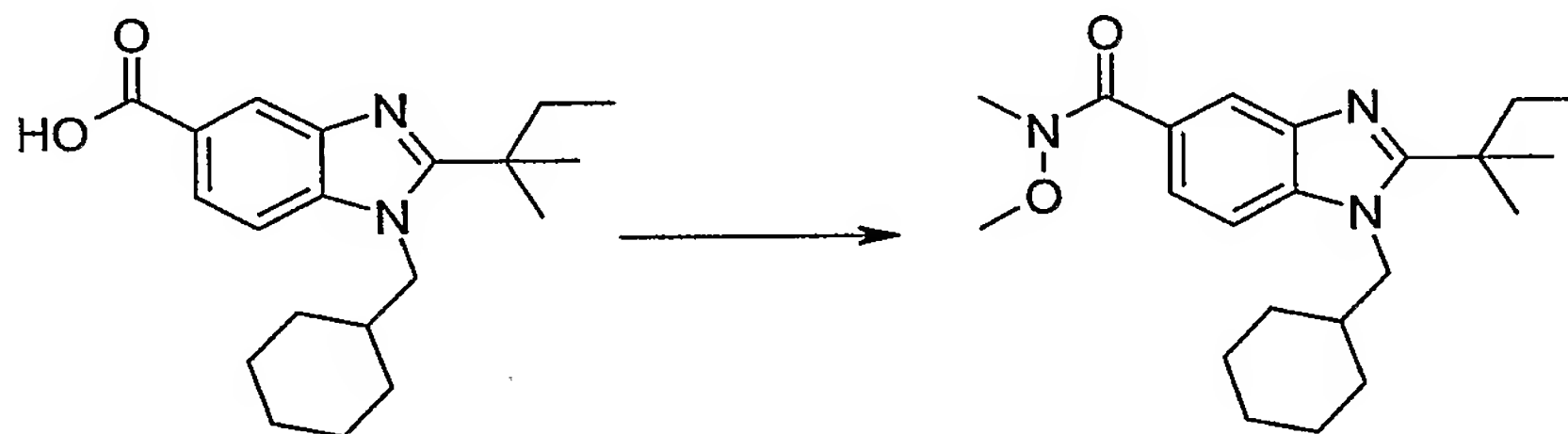
Methyl 2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazole-5-carboxylate (165 mg, 0.502 mmol) was dissolved in 10 mL of EtOH containing 2 mL of 1M LiOH. The solution was refluxed for 3h. The solution was cooled to RT and the solvent was concentrated. The solution was neutralized with 1M HCl and extracted with DCM and EtOAc. The combined organic phases were washed with brine and dried over anhydrous MgSO₄. The organic phases were combined and concentrated to afford a crude desired title compound which was used directly in Step A. Yield: 140 mg (87%). MS (ESI) (M+H)⁺ 315.0.

Example 4

1-(Cyclohexylmethyl)-2-(1,1-dimethylpropyl)-*N*-methoxy-*N*-methyl-1*H*-benzimidazole-5-carboxamide



Step A. 1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-*N*-methoxy-*N*-methyl-1*H*-benzimidazole-5-carboxamide

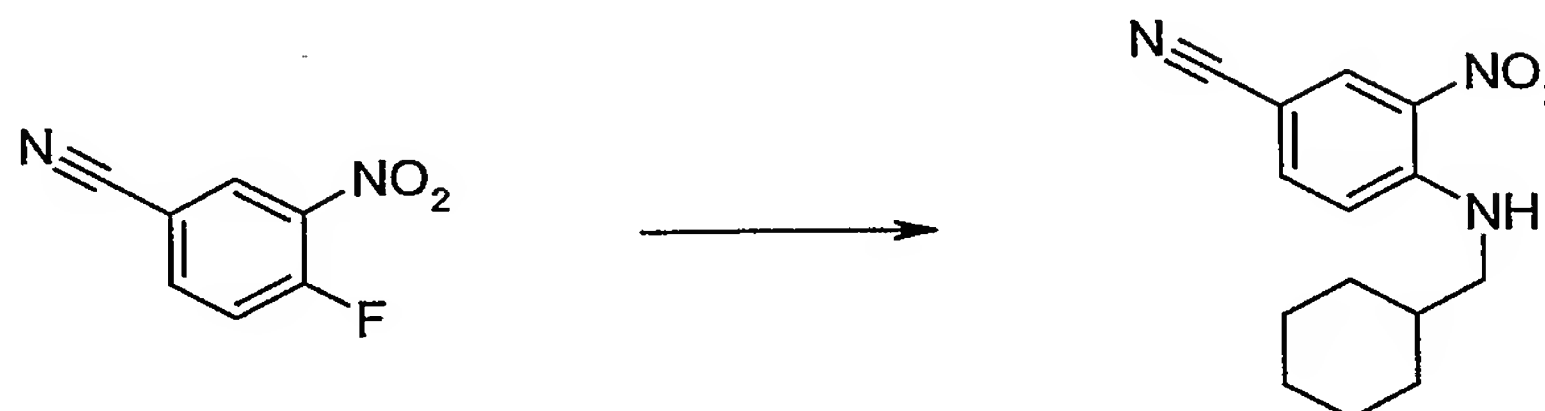


Following the same procedure in Example 3, Step A, using O,N-dimethylhydroxylamine hydrochloride (36.6 mg, 0.38 mmol), diisopropylethylamine (144 μ L, 106.6 mg, 0.83 mmol) and a solution of 1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazole-5-carboxylic acid (82.1 mg, 0.250 mmol) in DMF (5 mL) (for preparation, see the following Steps B, C, D and E) at 0 °C, and later, HATU (114.1 mg, 0.30 mmol). The mixture was stirred overnight at room temperature, added H₂O (50 mL), extracted with EtOAc (3x50 mL). The desired title compound was purified by reversed-phase HPLC (C-18 column) using 20-70% CH₃CN/H₂O to give 107.9 mg (89%) of a white solid. ¹H NMR (400 MHz, CD₃OD) δ 0.86 (t, J=7.52 Hz, 3 H), 1.26 (m, 5 H), 1.67 (m, 3 H), 1.69 (s, 6 H), 1.78 (m, 2 H), 2.04 (q, J=7.49 Hz, 2 H), 2.13 (m, 1 H), 3.41 (s, 3 H), 3.59 (s, 3 H), 4.51 (d, J=7.81 Hz, 2 H), 7.90 (dd,

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J=8.79, 1.37 Hz, 1 H), 8.01 (d, J=8.79 Hz, 1 H), 8.08 (d, J=0.78 Hz, 1 H). MS (ESI) (M+H)⁺ = 372.07.

Step B. 4-[(cyclohexylmethyl)amino]-3-nitro-benzonitrile

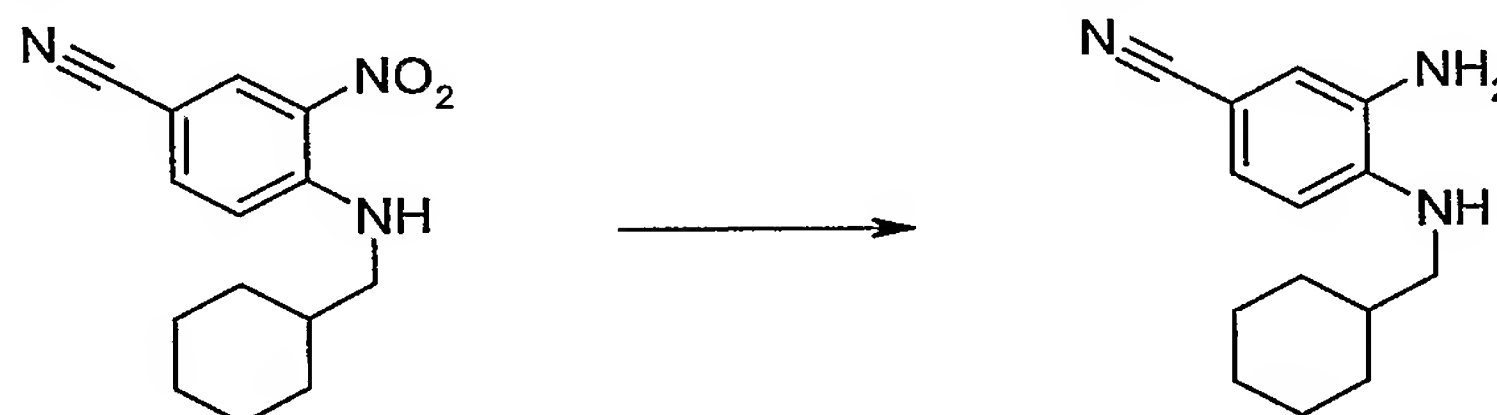


5

Cyclohexylmethylamine (3.12 mL, 2.72 g, 24.0 mmol) was added to a suspension of 4-fluoro-3-nitro-benzonitrile (3.22 g, 20.0 mmol) and sodium carbonate (4.66 g, 44.0 mmol) in EtOH (60 mL) at room temperature. The reaction mixture was stirred overnight, and diluted with H₂O (800 mL). The yellow solid was precipitated out and collected to give the desired

10 product (5.25 g, 100%). ¹H NMR (400 MHz, CDCl₃): δ 1.07 (m, 2 H), 1.25 (m, 3 H), 1.75 (m, 6 H), 3.19 (dd, J=6.64, 5.47 Hz, 2 H), 6.91 (d, J=8.98 Hz, 1 H), 7.59 (m, 1 H), 8.50 (s broad, 1 H), 8.51 (d, J=2.15 Hz, 1 H).

Step C. 3-amino-4-[(cyclohexylmethyl)amino]-benzonitrile

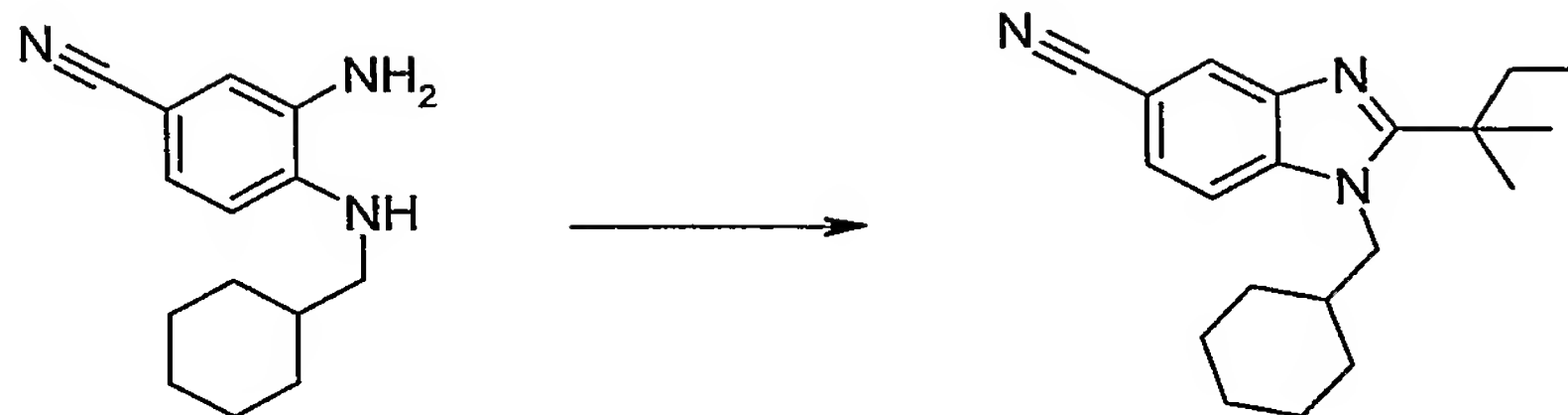


15 4-[(Cyclohexylmethyl)amino]-3-nitro-benzonitrile (5.25 g, 20.0 mmol) was hydrogenated in ethyl acetate (200 mL) catalyzed by 10% Pd/C (0.8 g) at 20-30 psi H₂ in Parr shaker for 2 h at room temperature. After the reaction was complete, the reaction mixture was filtered through celite. Removal of the solvent gave the desired title compound diamine (4.33 g, 94%) which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 1.02 (m, 2 H), 1.24 (m, 3 H), 1.62 (m, 1 H), 1.76 (m, 5 H), 3.00 (m, 2 H), 3.27 (s broad, 2 H), 4.05 (s broad, 1 H), 6.56 (d, J=8.20 Hz, 1 H), 6.93 (d, J=1.76 Hz, 1 H), 7.16 (dd, J=8.20, 1.95 Hz, 1 H). MS (ESI) (M+H)⁺ = 229.90 (M+1)⁺.

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Step D. 1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1H-benzimidazole-5-carbonitrile

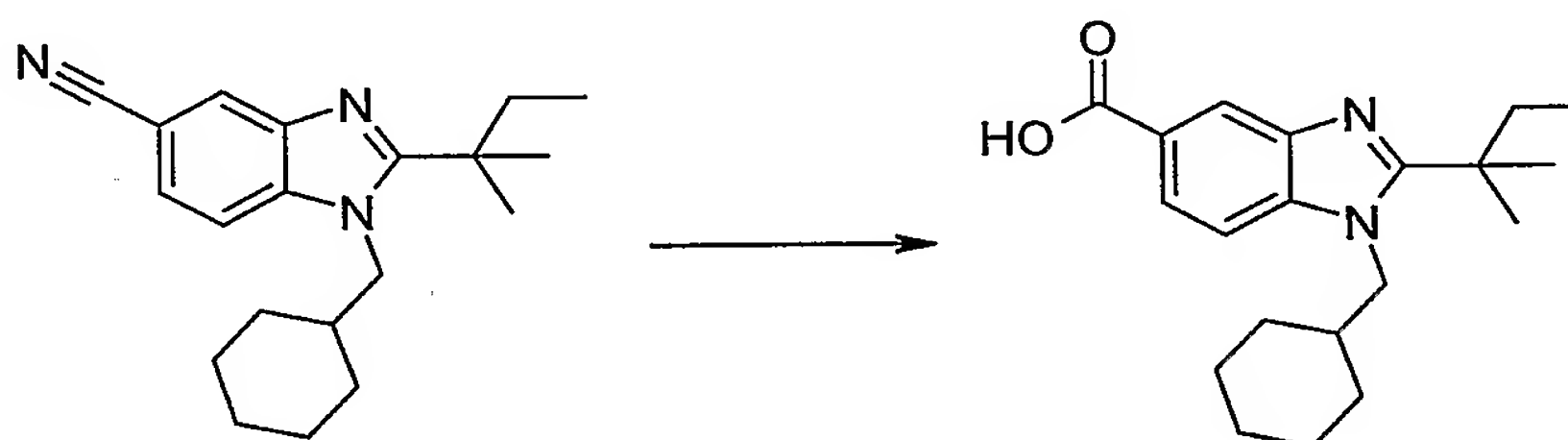
- 33 -



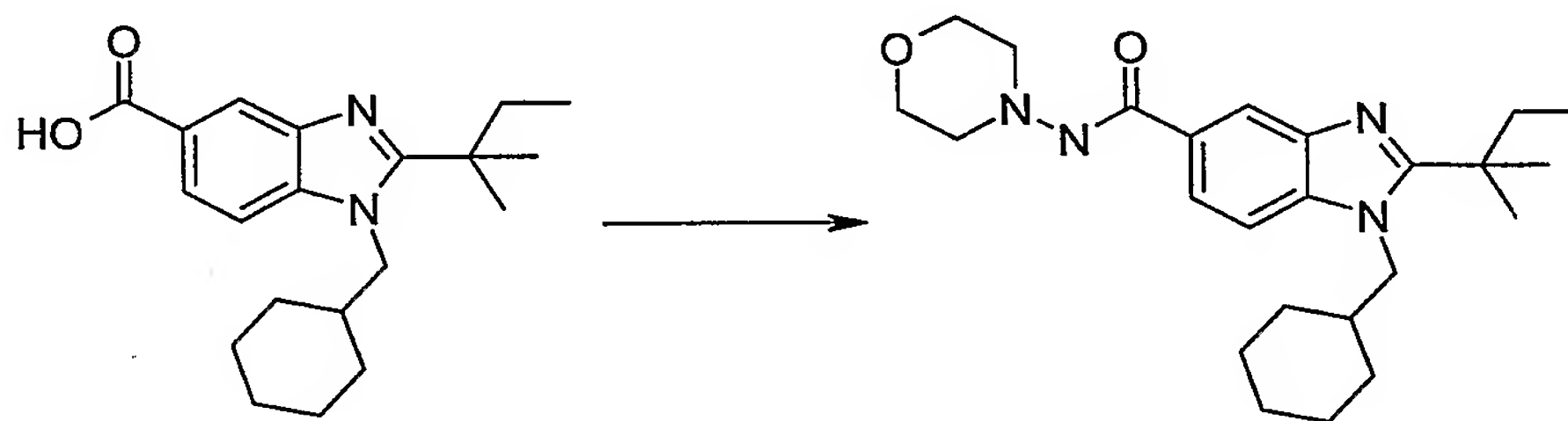
2,2-Dimethyl butyryl chloride (1.37 g, 10.18 mmol) was added dropwise to a stirring solution of 3-amino-4-[(cyclohexylmethyl)amino]benzonitrile (1.83 g, 7.98 mmol) and DMAP (387.8 mg, 3.17 mmol) in dichloromethane (70 mL) at 0 °C. The solution was stirred overnight at room temperature. After evaporation of the solvent, a crude product was obtained as a grey white solid (3.51 g, 100%). MS (ESI) (M+H)⁺ = 328.03.

This crude product (773.9 mg, 1.76 mmol) was dissolved in 1,2-dichloroethane (5x5 mL) in five Teflon-capped test tubes. The vessels were irradiated by microwave for 2 h at 190 °C, then, diluted with EtOAc (200 mL), washed with 2N NaOH (10 mL), sat. NaCl (2x10 mL) and dried over anhydrous Na₂SO₄. Upon filtration and concentration, the desired title compound was obtained as a white solid (623.1 mg, 100%). MS (ESI) (M+H)⁺ = 310.02.

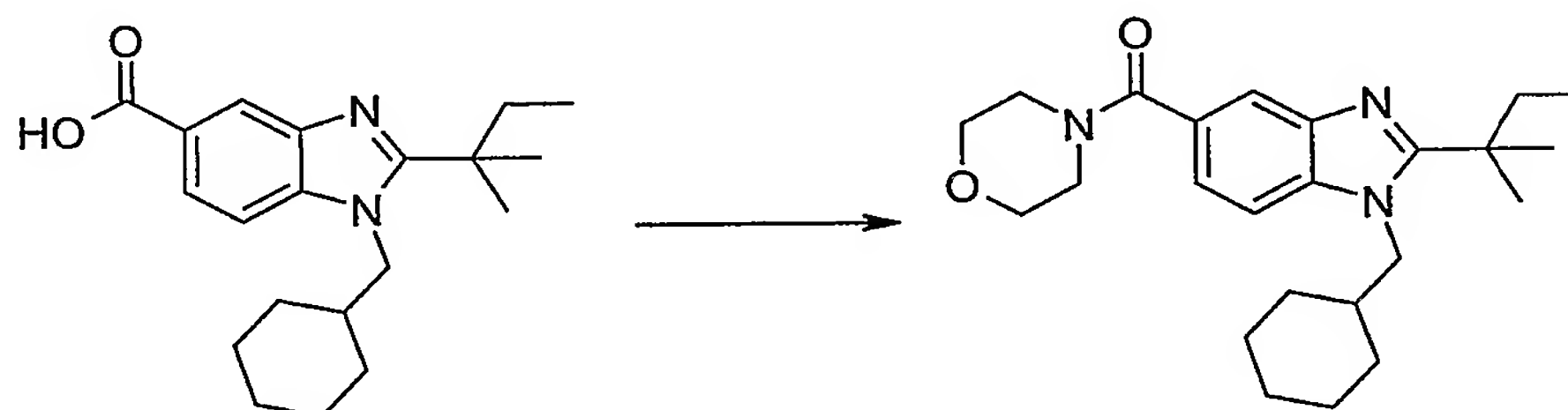
Step E. 1-(Cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1H-benzimidazole-5-carboxylic acid



A mixture 1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1H-benzimidazole-5-carbonitrile (623.1 mg, 1.76 mmol) and potassium hydroxide (620.1 mg, 11.05 mmol) in 20 mL of EtOH-H₂O (1:1) was heated for 24 h at reflux. Upon evaporation of ethanol, the aqueous solution was extracted with ether (2x50 mL) and then acidified with 2N HCl until pH=5-6. The desired title compound was obtained as a grey solid which was collected by filtration and drying *in vacuo*. Yield: 541.2 mg (94%). ¹H NMR (400 MHz, CD₃OD): δ 0.85 (t, J=7.52 Hz, 3 H), 1.26 (m, 5 H), 1.65 (m, 3 H), 1.69 (s, 6 H), 1.78 (s, 2 H), 2.04 (q, J=7.42 Hz, 2 H), 2.12 (m, 1 H), 4.50 (d, J=7.62 Hz, 2 H), 7.99 (m, 1 H), 8.24 (m, 1 H), 8.42 (d, J=0.98 Hz, 1 H). MS (ESI) (M+H)⁺ = 329.02.

Example 5**1-(Cyclohexylmethyl)-2-(1,1-dimethylpropyl)-*N*-morpholin-4-yl-1*H*-benzimidazole-5-carboxamide**

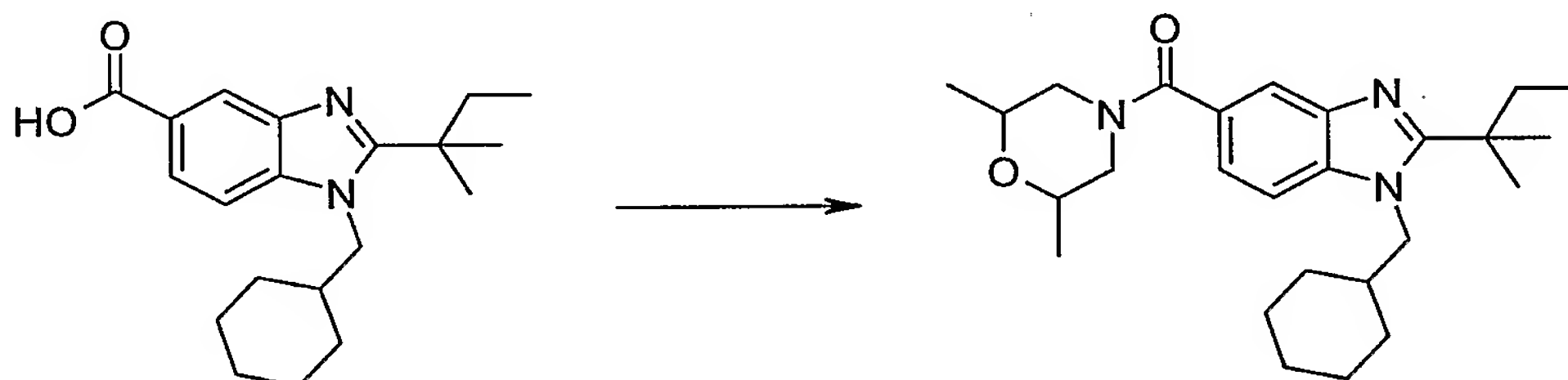
- 5 Following the same procedure in Example 3, Step A, using morpholin-4-amine (30.6 mg, 0.30 mmol), diisopropylethylamine (69.7 μ L, 51.7 mg, 0.40 mmol) and a solution of 1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazole-5-carboxylic acid (65.7 mg, 0.20 mmol) in DMF (5 mL) (for preparation, see in Example 4, Step E) at 0 °C, and later, HATU (91.3 mg, 0.24 mmol). The mixture was stirred overnight at room temperature, added
- 10 H₂O (50 mL), extracted with EtOAc (3x50 mL). The desired title compound was purified by reversed-phase HPLC (C-18 column) using 10-50% CH₃CN/H₂O to give 79.2 mg (75%) of a white solid. ¹H NMR (400 MHz, CD₃OD): δ 0.86 (t, *J*=7.52 Hz, 3 H), 1.26 (m, 5 H), 1.64 (m, 3 H), 1.70 (s, 6 H), 1.78 (m, 2 H), 2.04 (q, *J*=7.49 Hz, 2 H), 2.13 (m, 1 H), 2.96 (m, 4 H), 3.83 (m, 4 H), 4.51 (d, *J*=7.62 Hz, 2 H), 8.03 (m, 2 H), 8.22 (m, 1 H). MS (ESI) (*M*+*H*)⁺ = 413.3.
- 15 Anal. Calcd for C₂₄H₃₆N₄O₂+1.90 TFA+1.30 H₂O + 0.30 MeCN (664.96): C, 51.30; H, 6.28; N, 9.06. Found: C, 51.33; H, 6.21; N, 9.08.

Example 6**1-(Cyclohexylmethyl)-2-(1,1-dimethylpropyl)-5-(morpholin-4-ylcarbonyl)-1*H*-benzimidazole**

Following the same procedure in Example 3, Step A, using morpholine (26.1 mg, 0.30 mmol), diisopropylethylamine (69.7 μ L, 51.7 mg, 0.40 mmol) and a solution of 1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazole-5-carboxylic acid (65.7 mg,

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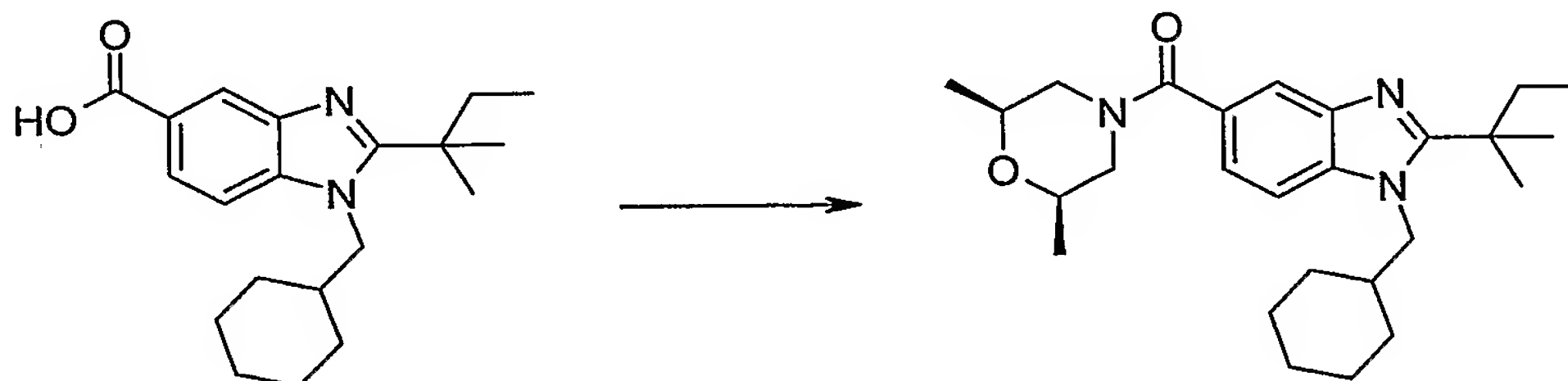
0.20 mmol)) (for preparation, see in Example 4, Step E) in DMF (5 mL) at 0 °C, and later, HATU (91.3 mg, 0.24 mmol). The mixture was stirred overnight at room temperature, added H₂O (50 mL), extracted with EtOAc (3x50 mL). The desired title compound was purified by reversed-phase HPLC (C-18 column) using 10-50% CH₃CN/H₂O to give 82.1 mg (80%) of a white solid. ¹H NMR (400 MHz, CD₃OD): δ 0.86 (t, J=7.42 Hz, 3 H), 1.27 (m, 5 H), 1.65 (m, 3 H), 1.69 (s, 6 H), 1.78 (m, 2 H), 2.04 (q, J=7.42 Hz, 2 H), 2.12 (m, 1 H), 3.47 (m, 2 H), 3.62 (m, 2 H), 3.79 (m, 4 H), 4.50 (d, J=7.62 Hz, 2 H), 7.66 (dd, J=8.69, 1.46 Hz, 1 H), 7.82 (d, J=0.78 Hz, 1 H), 8.01 (d, J=8.79 Hz, 1 H). MS (ESI) (M+H)⁺ = 398.3. Anal. Calcd for C₂₄H₃₅N₃O₂+1.60 TFA+1.10 H₂O +0.30 MeCN (612.14): C, 54.55; H, 6.54; N, 7.55. Found: C, 54.61; H, 6.53; N, 7.51.

Example 7**1-(Cyclohexylmethyl)-5-[(2,6-dimethylmorpholin-4-yl)carbonyl]-2-(1,1-dimethylpropyl)-1H-benzimidazole**

15

Following the same procedure in Example 3, Step A, using 2,6-dimethylmorpholine (34.6 mg, 0.30 mmol), diisopropylethylamine (69.7 µL, 51.7 mg, 0.40 mmol) and a solution of 1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1H-benzimidazole-5-carboxylic acid (66.8 mg, 0.203 mmol) (for preparation, see in Example 4, Step E) in DMF (5 mL) at 0 °C, and later, HATU (91.3 mg, 0.24 mmol). The mixture was stirred overnight at room temperature, added H₂O (50 mL), extracted with EtOAc (3x50 mL). The desired title compound was purified by MPLC (hex/EtOAc 1:1 as eluent on silica gel) to give 76.0 mg (89%) of a white solid. ¹H NMR (400 MHz, CD₃OD): δ 0.86 (t, J=7.52 Hz, 3 H), 1.04 (m, 3 H), 1.27 (m, 8 H), 1.66 (m, 2 H), 1.69 (s, 6 H), 1.71 (m, 1 H), 1.79 (m, 2 H), 2.04 (q, J=7.55 Hz, 2 H), 2.13 (m, 1 H), 2.63 (m, 1 H), 2.92 (m, 1 H), 3.59 (m, 3 H), 4.50 (d, J=7.81 Hz, 2 H), 4.54 (m, 1 H), 7.65 (dd, J=8.69, 1.46 Hz, 1 H), 7.81 (d, J=0.78 Hz, 1 H), 8.01 (d, J=8.59 Hz, 1 H). MS (ESI) (M+H)⁺ = 426.2. Anal. Calcd for C₂₆H₃₉N₃O₂+1.70 TFA+0.20 H₂O (623.06): C, 56.68; H, 6.65; N, 6.74. Found: C, 56.68; H, 6.59; N, 6.81.

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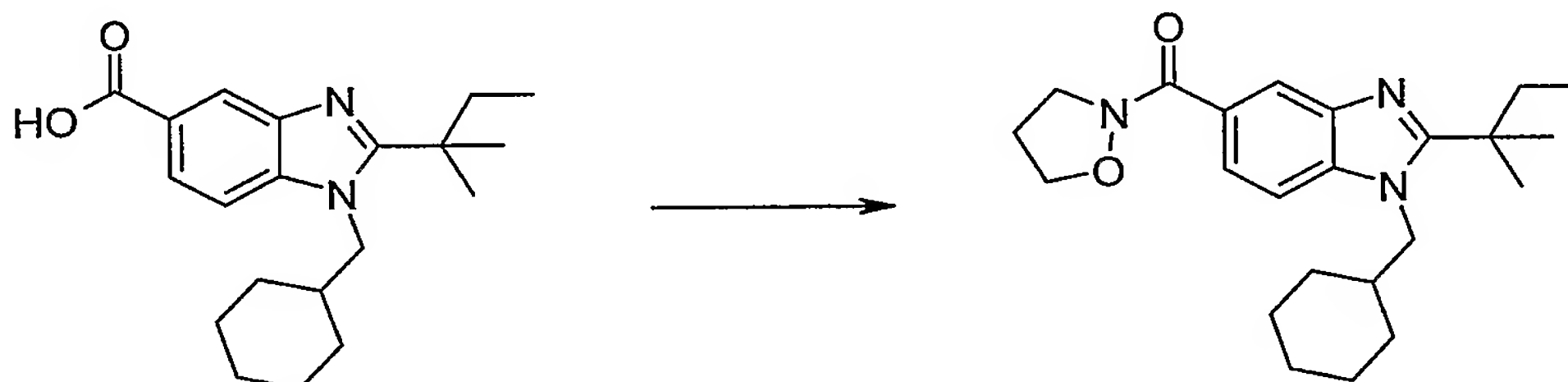
Example 8**1-(Cyclohexylmethyl)-5-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]carbonyl}-2-(1,1-dimethylpropyl)-1*H*-benzimidazole**

5

Following the same procedure in Example 3, Step A, using (2*R*,6*S*)-2,6-dimethylmorpholine (34.6 mg, 0.30 mmol), diisopropylethylamine (69.7 μ L, 51.7 mg, 0.40 mmol) and a solution of 1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazole-5-carboxylic acid (65.9 mg, 0.20 mmol) (for preparation, see in Example 4, Step E) in DMF (5 mL) at 0 $^{\circ}$ C, and later, HATU (91.3 mg, 0.24 mmol). The mixture was stirred overnight at room temperature, added H₂O (50 mL), extracted with EtOAc (3x50 mL). The desired title compound was purified by MPLC (hex/EtOAc 1:1 as eluent on silica gel) to give 75.7 mg (89%) of a white solid. ¹H NMR (400 MHz, CD₃OD): δ 0.86 (t, *J*=7.52 Hz, 3 H), 1.04 (m, 3 H), 1.28 (m, 8 H), 1.66 (m, 2 H), 1.69 (s, 6 H), 1.71 (m, 1 H), 1.79 (m, 2 H), 2.04 (q, *J*=7.42 Hz, 2 H), 2.13 (m, 1 H), 2.63 (m, 1 H), 2.92 (m, 1 H), 3.58 (m, 3 H), 4.50 (d, *J*=7.62 Hz, 2 H), 4.55 (m, 1 H), 7.65 (dd, *J*=8.69, 1.46 Hz, 1 H), 7.81 (d, *J*=0.78 Hz, 1 H), 8.01 (d, *J*=8.79 Hz, 1 H). MS (ESI) (*M*+H)⁺ = 426.2. Anal. Calcd for C₂₆H₃₉N₃O₂+1.60 TFA+0.30 H₂O (613.46): C, 57.17; H, 6.77; N, 6.85. Found: C, 57.18; H, 6.69; N, 6.88.

10
15**Example 9****1-(Cyclohexylmethyl)-2-(1,1-dimethylpropyl)-5-(isoxazolidin-2-ylcarbonyl)-1*H*-benzimidazole**

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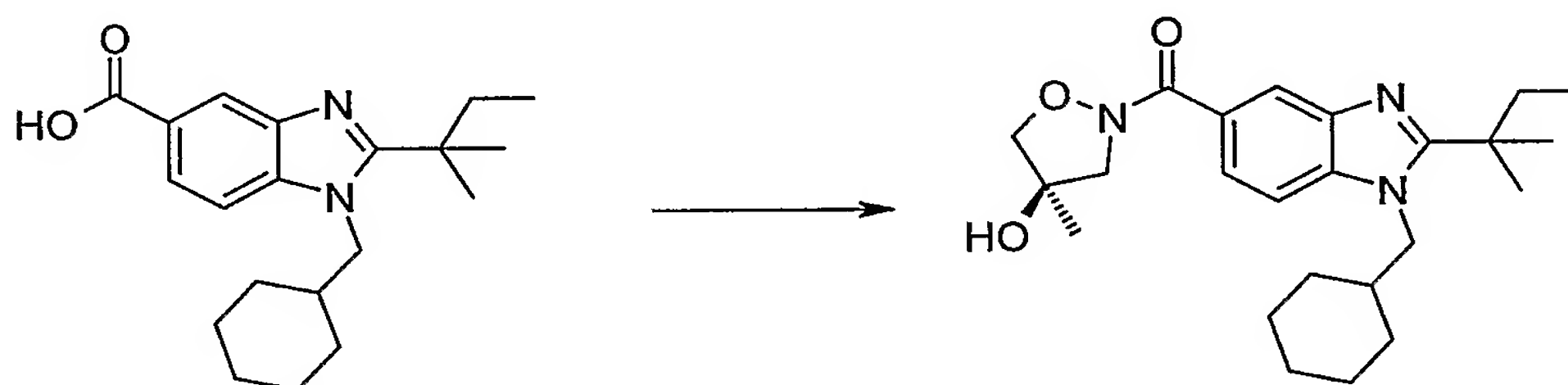
Following the same procedure in Example 3, Step A, using isoxazolidine hydrochloride (29.5 mg, 0.26 mmol), diisopropylethylamine (144 μ L, 106.6 mg, 0.83 mmol) and a solution of 1-

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(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazole-5-carboxylic acid (82.1 mg, 0.25 mmol) (for preparation, see in Example 4, Step E) in DMF (5 mL) at 0 °C, and later, HATU (114.0 mg, 0.30 mmol). The mixture was stirred for 4h at room temperature, and quenched by adding H₂O (5 mL). Upon evapoarton, the desired title compound was purified by reversed-phase HPLC (C-18 column) using 20-50% CH₃CN/H₂O to give 94.8 mg (76%) of a white solid. ¹H NMR (400 MHz, CD₃OD): δ 0.86 (t, J=7.42 Hz, 3 H), 1.27 (m, 5 H), 1.66 (m, 3 H), 1.69 (s, 6 H), 1.79 (m, 2 H), 2.04 (q, J=7.49 Hz, 2 H), 2.13 (m, 1 H), 2.43 (m, 2 H), 3.94 (m, 2 H), 4.07 (t, J=6.74 Hz, 2 H), 4.50 (d, J=7.62 Hz, 2 H), 8.00 (m, 2 H), 8.19 (s, 1 H). MS (ESI) (M+H)⁺ = 384.2. Anal. Calcd for C₂₃H₃₃N₃O₂+1.40 TFA+1.30 H₂O (566.59): C, 54.69; H, 6.58; N, 7.42. Found: C, 54.66; H, 6.50; N, 7.68.

Example 10

(4*R*)-2-[[1-(Cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazol-5-yl]carbonyl]-4-methylisoxazolidin-4-ol



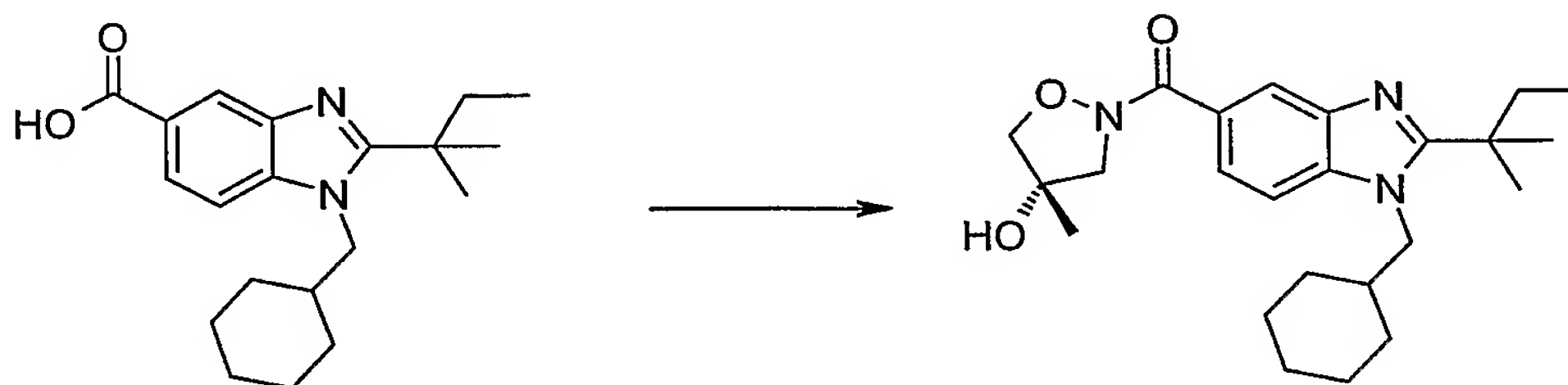
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Following the same procedure in Example 3, Step A, using (4*R*)-4-methylisoxazolidin-4-ol hydrochloride (36.0 mg, 0.25 mmol), diisopropylethylamine (144 μL, 106.6 mg, 0.83 mmol) and a solution of 1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazole-5-carboxylic acid (82.1 mg, 0.25 mmol) (for preparation, see in Example 4, Step E) in DMF (5 mL) at 0 °C, and later, HATU (114.0 mg, 0.30 mmol). The mixture was stirred for 4h at room temperature, added H₂O (5 mL). Upon evapoarton, the desired title compound was purified by reversed-phase HPLC (C-18 column) using 20-50% CH₃CN/H₂O to give 90.5 mg (69%) of a white solid. [α]_D: +16.6 ° (c 0.15, EtOH). ¹H NMR (400 MHz, CD₃OD): δ 0.86 (t, J=7.42 Hz, 3 H), 1.26 (m, 5 H), 1.50 (s, 3 H), 1.66 (m, 3 H), 1.69 (s, 6 H), 1.79 (m, 2 H), 2.04 (q, J=7.49 Hz, 2 H), 2.13 (m, 1 H), 3.82 (d, J=11.33 Hz, 1 H), 3.89 (d, J=8.40 Hz, 1 H), 3.97 (m, 2 H), 4.50 (d, J=7.81 Hz, 2 H), 7.99 (m, 2 H), 8.19 (s, 1 H). MS (ESI) (M+H)⁺ = 414.2. Anal. Calcd for C₂₄H₃₅N₃O₃+1.50 TFA+1.10 H₂O (604.42): C, 53.65; H, 6.45; N, 6.95. Found: C, 53.55; H, 6.44; N, 7.18.

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Example 11

(4S)-2-[[1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1H-benzimidazol-5-yl]carbonyl]-4-methylisoxazolidin-4-ol



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Following the same procedure in Example 3, Step A, using (4S)-4-methylisoxazolidin-4-ol hydrochloride (36.8 mg, 0.264 mmol), diisopropylethylamine (144 μ L, 106.6 mg, 0.83 mmol) and a solution of 1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1H-benzimidazole-5-carboxylic acid (83.2 mg, 0.253 mmol) (for preparation, see in Example 4, Step E) in DMF (5 mL) at 0 $^{\circ}$ C, and later, HATU (114.0 mg, 0.30 mmol). The mixture was stirred for 4h at room temperature, and quenched by adding H₂O (5 mL). Upon evapoarton, the desired title compound was purified by reversed-phase HPLC (C-18 column) using 20-50% CH₃CN/H₂O to give 74.9mg (56%) of a white solid. $[\alpha]_D$: -14.1 $^{\circ}$ (c 0.17, EtOH). ¹H NMR (400 MHz, CD₃OD): δ 0.85 (t, J=7.52 Hz, 3 H), 1.27 (m, 5 H), 1.50 (s, 3 H), 1.66 (m, 3 H), 1.69 (s, 6 H), 1.79 (m, 2 H), 2.04 (q, J=7.42 Hz, 2 H), 2.13 (m, 1 H), 3.82 (d, J=11.33 Hz, 1 H), 3.89 (d, J=8.40 Hz, 1 H), 3.97 (m, 2 H), 4.50 (d, J=7.62 Hz, 2 H), 7.99 (m, 2 H), 8.18 (s, 1 H). MS (ESI) (M+H)⁺ = 414.2. Anal. Calcd for C₂₄H₃₅N₃O₃+1.30 TFA+2.00 H₂O (597.83): C, 53.44; H, 6.79; N, 7.03. Found: C, 53.39; H, 6.64; N, 7.22.

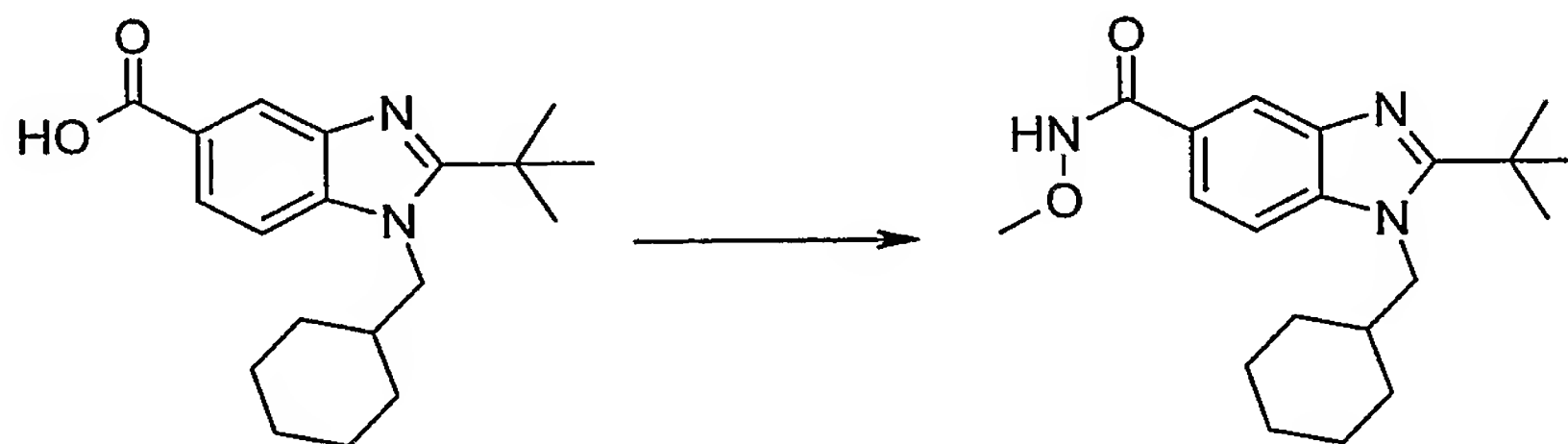
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Example 12

2-tert-Butyl-1-(cyclohexylmethyl)-N-methoxy-1H-benzimidazole-5-carboxamide

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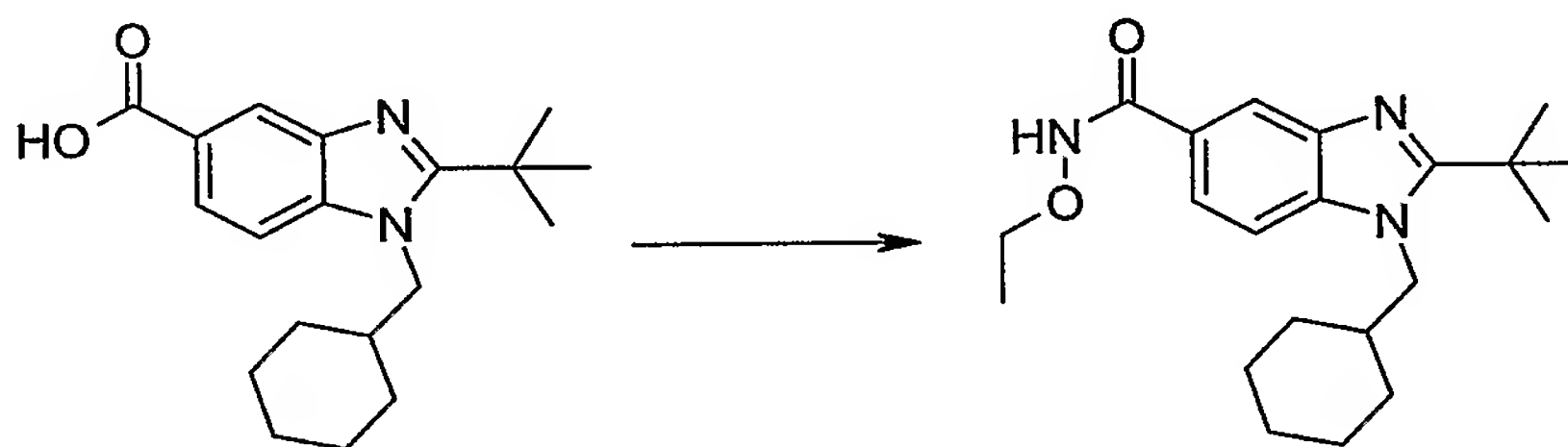
Following the same procedure in Example 3, Step A, using 2-tert-butyl-1-(cyclohexylmethyl)-1H-benzimidazole-5-carboxylic acid (50 mg, 0.159 mmol) (for

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preparation, see Steps B to F in Example 3), methoxylamine hydrochloride (26 mg, 0.318 mmol), HATU (75 mg, 0.191 mmol) and diisopropylethylamine (0.085 mL, 0.318 mmol) in 5 mL of DMF. The product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O on a C-18 column and then lyophilized affording the desired title compound as the corresponding TFA salt. Yield: 56 mg (77%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.24 (m, 5 H), 1.62 (m, 2 H), 1.68 (s, 10 H), 1.76 (m, 2 H), 2.11 (m, 1 H), 3.83 (s, 3 H), 4.48 (d, J=7.62 Hz, 2 H), 7.93 (dd, J=8.79, 1.56 Hz, 1 H), 7.98 (m, 1 H), 8.18 (dd, J=1.56, 0.78 Hz, 1 H); MS (ESI) (M+H)⁺ 344.3; Anal. Calcd for C₂₀H₂₉N₃O₂ + 1.6 TFA + 0.6 H₂O: C, 51.92; H, 5.97; N, 7.83. Found: C, 51.85; H, 6.02; N, 7.78.

10 Example 13:

2-*tert*-Butyl-1-(cyclohexylmethyl)-N-ethoxy-1H-benzimidazole-5-carboxamide



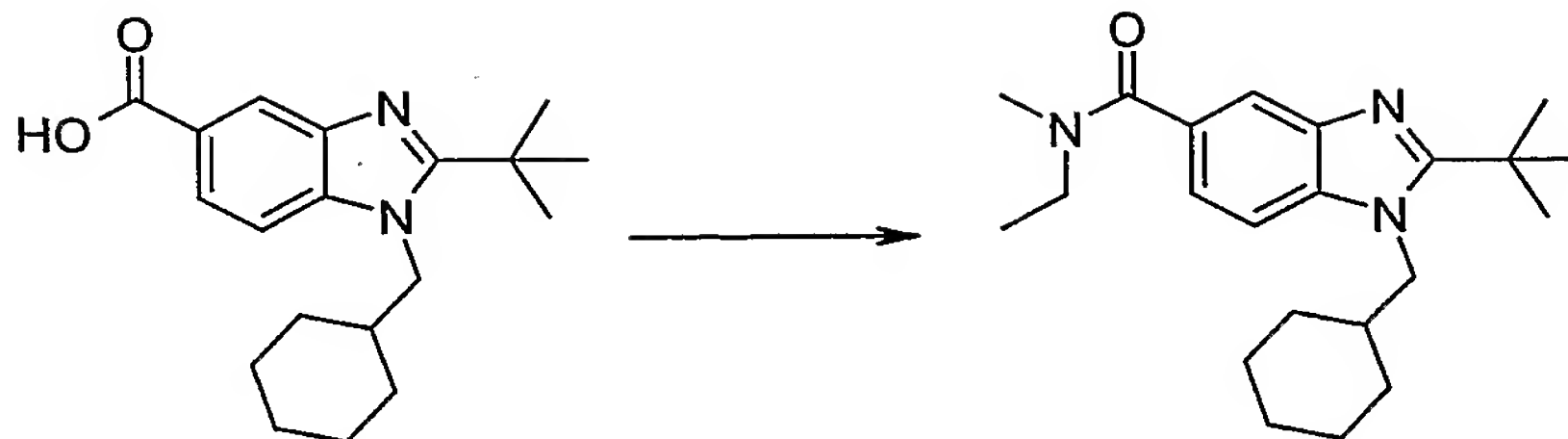
Following the same procedure in Example 3, Step A, using 2-*tert*-butyl-1-

(cyclohexylmethyl)-1H-benzimidazole-5-carboxylic acid (TFA salt) (100 mg, 0.233 mmol) (for preparation, see Steps B to F in Example 3), O-ethylhydroxylamine hydrochloride (35 mg, 0.350 mmol), HATU (110 mg, 0.280 mmol) and diisopropylethylamine (0.145 mL, 0.816 mmol) in 5 mL of DMF. The product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O on a C-18 column and then lyophilized affording the desired title compound as the corresponding TFA salt. Yield: 73 mg (66%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.25 (m, 5 H), 1.33 (t, J=7.03 Hz, 3 H), 1.64 (m, 2 H), 1.69 (s, 10 H), 1.78 (m, 2 H), 2.13 (m, 1 H), 4.06 (q, J=7.03 Hz, 2 H), 4.50 (d, J=7.62 Hz, 2 H), 7.95 (dd, J=7.23, 1.56 Hz, 1 H), 8.00 (m, 1 H), 8.19 (d, J=0.78 Hz, 1 H); MS (ESI) (M+H)⁺ 358.3; Anal. Calcd for C₂₁H₃₁N₃O₂ + 1.5 TFA + 1.0 H₂O: C, 52.74; H, 6.36; N, 7.69. Found: C, 52.74; H, 6.50; N, 7.54.

25 Example 14

2-*tert*-Butyl-1-(cyclohexylmethyl)-N-ethyl-N-methyl-1H-benzimidazole-5-carboxamide

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Following the same procedure in Example 3, Step A, using 2-*tert*-butyl-1-

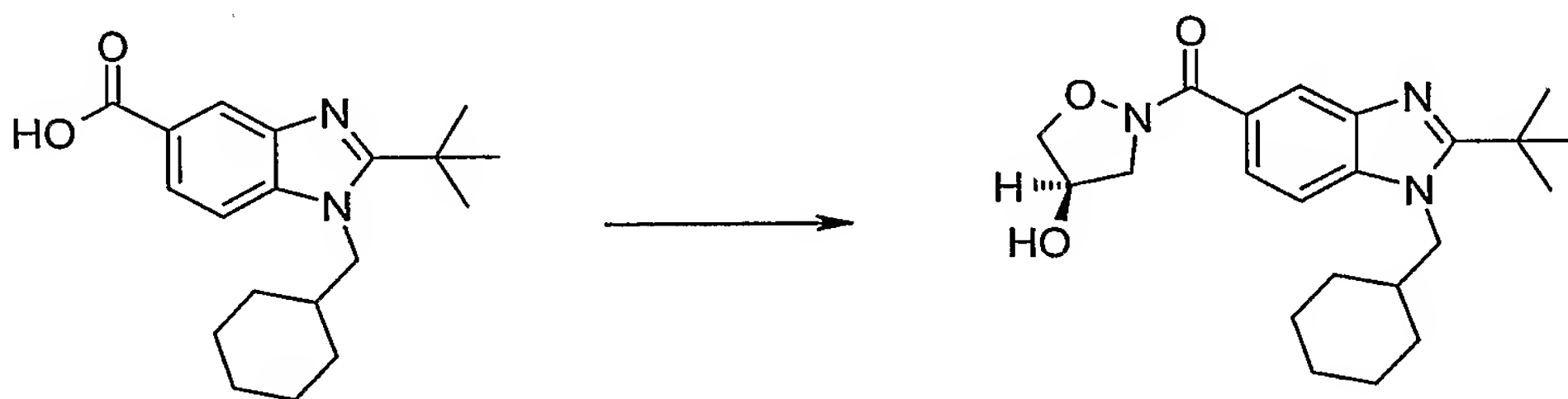
(cyclohexylmethyl)-1*H*-benzimidazole-5-carboxylic acid (TFA salt) (47 mg, 0.110 mmol)

5 (for preparation, see Steps B to F in Example 3), *N*-ethylmethylamine (0.015 mL, 0.165 mmol), HATU (50 mg, 0.132 mmol) and diisopropylethylamine (0.030 mL, 0.165 mmol) in 5 mL of DMF. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O on a C-18 column and then lyophilized affording the desired title compound as the corresponding TFA salt. Yield: 45 mg (87%). ¹H NMR (400 MHz, METHANOL-D₄): δ

10 1.17 (t, *J*=6.93 Hz, 2 H), 1.26 (m, 8 H), 1.66 (m, 2 H), 1.70 (s, 9 H), 1.79 (m, 2 H), 2.14 (m, 1 H), 2.99 (s, 1 H), 3.12 (s, 1 H), 3.33 (d, *J*=7.03 Hz, 1 H), 3.63 (q, *J*=7.03 Hz, 1 H), 4.50 (d, *J*=7.62 Hz, 2 H), 7.63 (t, *J*=8.01 Hz, 1 H), 7.79 (d, *J*=4.49 Hz, 1 H), 8.00 (d, *J*=8.59 Hz, 1 H); MS (ESI) (*M*+H)⁺ 356.3; Anal. Calcd for C₂₂H₃₃N₃O + 1.2 TFA + 0.5 H₂O: C, 58.45; H, 7.08; N, 8.38. Found: C, 58.44; H, 7.09; N, 8.39.

15 Example 15

(4*R*)-2-{[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbonyl}isoxazolidin-4-ol



20

Following the same procedure in Example 3, Step A, using 2-*tert*-butyl-1-

(cyclohexylmethyl)-1*H*-benzimidazole-5-carboxylic acid (lithium salt) (50 mg, 0.156 mmol)

(for preparation, see Steps B to F in Example 3), (4*R*)-isoxazolidin-4-ol hydrochloride (21

mg, 0.172 mmol), HATU (71 mg, 0.187 mmol) and diisopropylethylamine (0.065 mL, 0.390

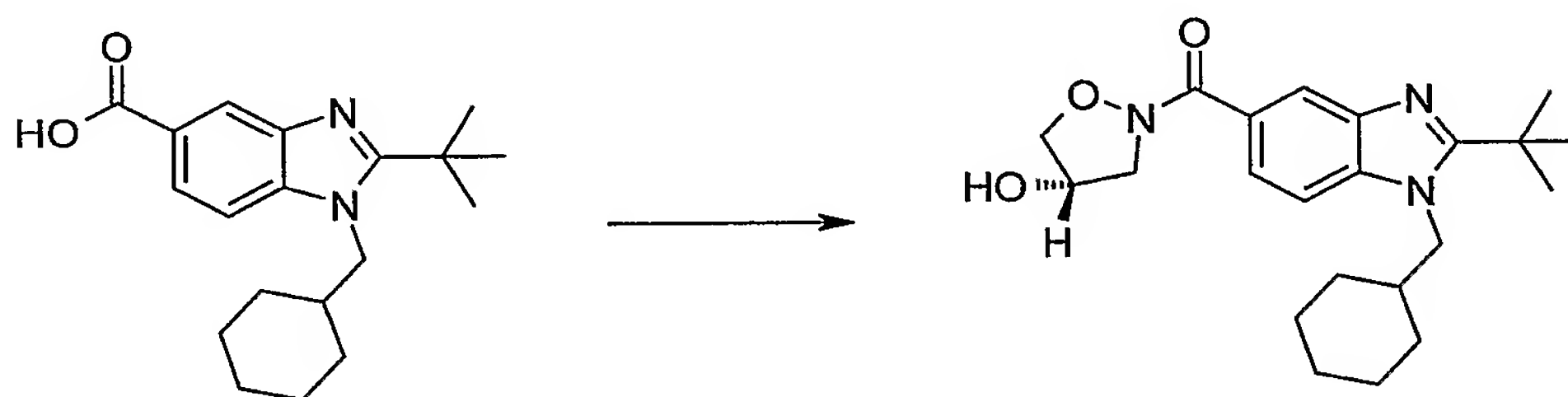
25 mmol) in 2 mL of DMF. The product was purified by reversed-phase HPLC using 20-80%

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CH₃CN/H₂O on a C-18 column and then lyophilized affording the desired title compound as the corresponding TFA salt. Yield: 56 mg (72%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.26 (m, 5 H), 1.66 (m, 2 H), 1.70 (s, 10 H), 1.79 (m, 2 H), 2.14 (m, 1 H), 3.84 (d, J=11.91 Hz, 1 H), 4.00 (d, J=8.20 Hz, 1 H), 4.07 (m, 2 H), 4.51 (d, J=7.62 Hz, 2 H), 4.82 (m, 1 H), 8.00 (m, 2 H), 8.20 (s, 1 H); MS (ESI) (M+H)⁺ 386.2; Anal. Calcd for C₂₂H₃₁N₃O₃ + 1.5 TFA: C, 53.95; H, 5.89; N, 7.55. Found: C, 53.93; H, 5.74; N, 7.60.

Example 16

(4*S*)-2-{{[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbonyl}isoxazolidin-4-ol



Following the same procedure in Example 3, Step A, using 2-*tert*-butyl-1-

(cyclohexylmethyl)-1*H*-benzimidazole-5-carboxylic acid (lithium salt) (50 mg, 0.156 mmol)

(for preparation, see Steps B to F in Example 3), (4*S*)-isoxazolidin-4-ol hydrochloride (21 mg, 0.172 mmol), HATU (71 mg, 0.187 mmol) and diisopropylethylamine (0.065 mL, 0.390 mmol) in 2 mL of DMF. The product was purified by reversed-phase HPLC using 20-80%

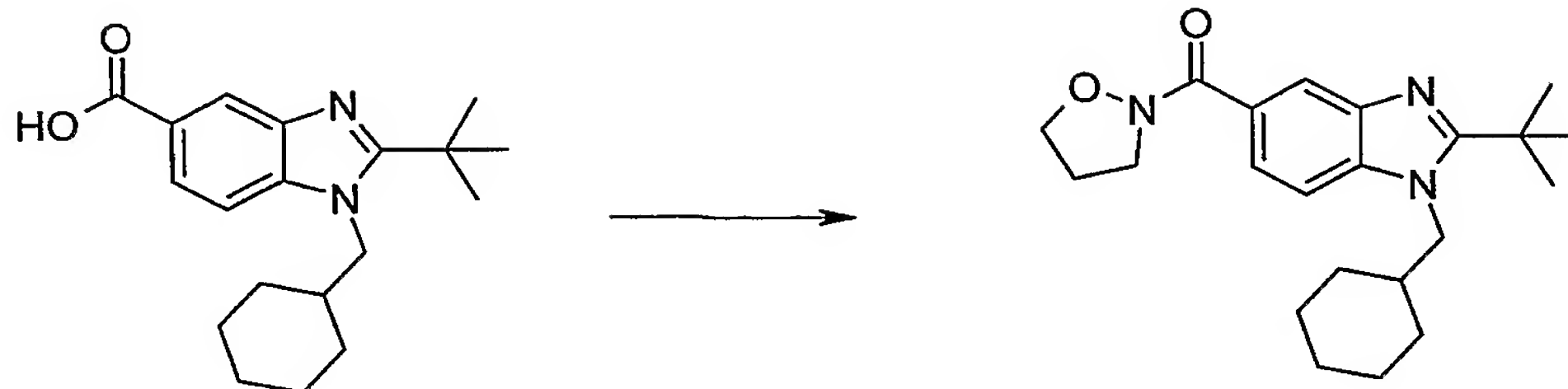
CH₃CN/H₂O on a C-18 column and then lyophilized affording the desired title compound as the corresponding TFA salt. Yield: 58 mg (74%). ¹H NMR (400 MHz, METHANOL-D₄): δ

1.26 (m, 5 H), 1.66 (m, 2 H), 1.70 (s, 10 H), 1.79 (m, 2 H), 2.15 (m, 1 H), 3.84 (d, J=12.11 Hz, 1 H), 3.99 (d, J=8.01 Hz, 1 H), 4.07 (m, 2 H), 4.51 (d, J=7.62 Hz, 2 H), 4.82 (m, 1 H), 8.00 (m, 2 H), 8.19 (m, 1 H); MS (ESI) (M+H)⁺ 386.2; Anal. Calcd for C₂₂H₃₁N₃O₃ + 1.3 TFA + 0.8 H₂O: C, 53.90; H, 6.23; N, 7.67. Found: C, 53.86; H, 6.30; N, 7.65.

Example 17

2-*tert*-Butyl-1-(cyclohexylmethyl)-5-(isoxazolidin-2-ylcarbonyl)-1*H*-benzimidazole

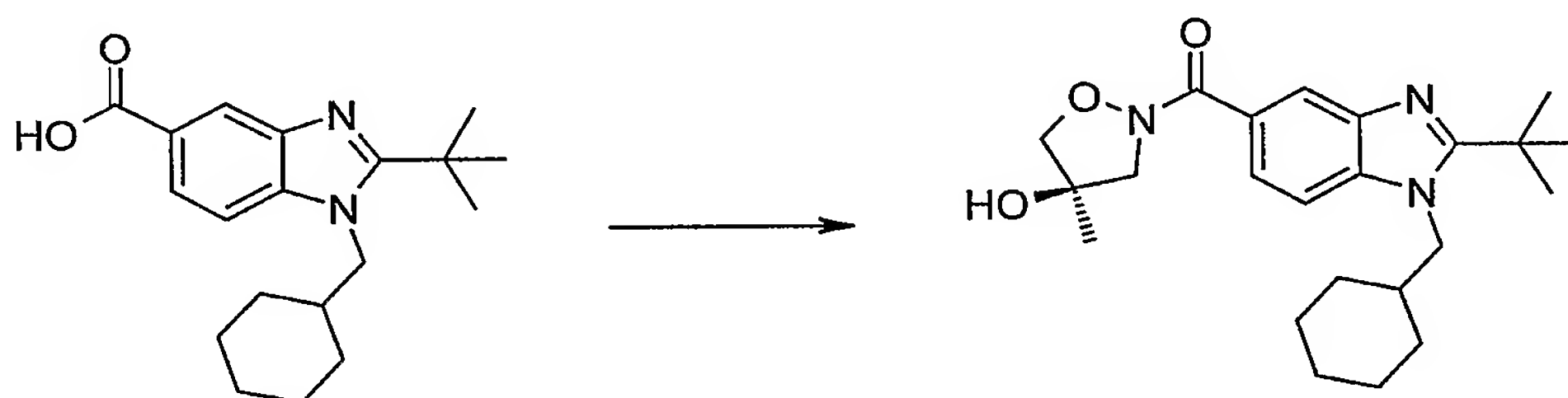
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Following the same procedure in Example 3, Step A, using 2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazole-5-carboxylic acid (lithium salt) (50 mg, 0.156 mmol) (for preparation, see Steps B to F in Example 3), isoxazolidine hydrochloride (19 mg, 0.172 mmol), HATU (71 mg, 0.187 mmol) and diisopropylethylamine (0.065 mL, 0.390 mmol) in 2 mL of DMF. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O on a C-18 column and then lyophilized affording the desired title compound as the corresponding TFA salt. Yield: 72 mg (95%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.26 (m, 5 H), 1.65 (m, 1 H), 1.67 (m, 1 H), 1.70 (s, 9 H), 1.79 (m, 2 H), 2.14 (m, 1 H), 2.43 (m, 2 H), 3.93 (m, 2 H), 4.07 (t, J=6.74 Hz, 2 H), 4.51 (d, J=7.62 Hz, 2 H), 8.00 (m, 2 H), 8.19 (s, 1 H); MS (ESI) (M+H)⁺ 370.2; Anal. Calcd for C₂₂H₃₁N₃O₂ + 1.7 TFA + 0.6 H₂O: C, 53.14; H, 5.95; N, 7.32. Found: C, 53.19; H, 5.95; N, 7.41.

Example 18

(4*R*)-2-{[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbonyl}-4-methylisoxazolidin-4-ol



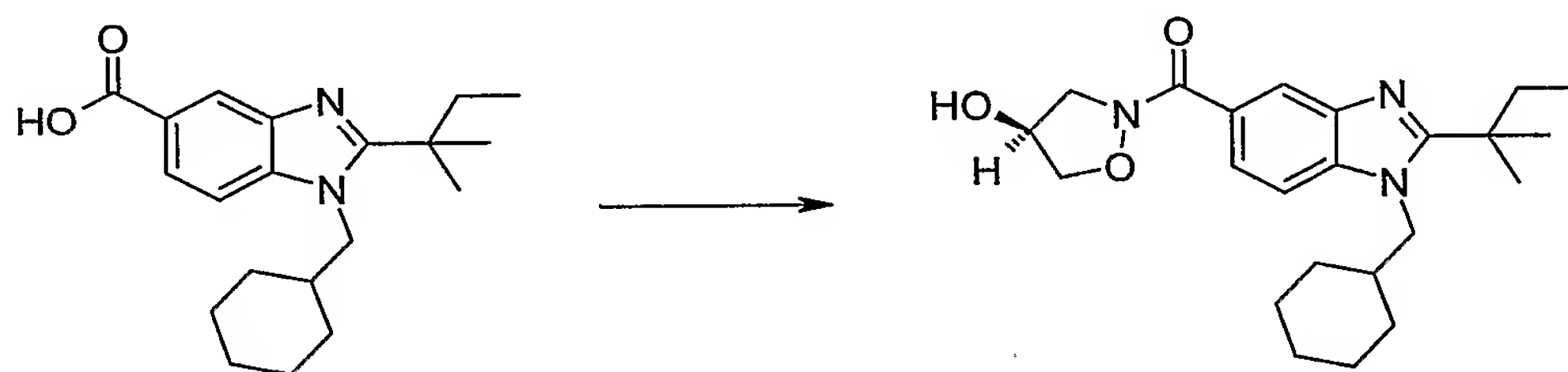
Following the same procedure in Example 3, Step A, using 2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazole-5-carboxylic acid (lithium salt) (50 mg, 0.156 mmol) (for preparation, see Steps B to F in Example 3), (4*R*)-4-methylisoxazolidin-4-ol hydrochloride (24 mg, 0.172 mmol), HATU (71 mg, 0.187 mmol) and diisopropylethylamine (0.065 mL, 0.390 mmol) in 2 mL of DMF. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O on a C-18 column and then lyophilized affording the

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desired title compound as the corresponding TFA salt. Yield: 63 mg (79%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.26 (m, 5 H), 1.50 (s, 3 H), 1.65 (m, 3 H), 1.70 (s, 9 H), 1.79 (m, 2 H), 2.14 (m, 1 H), 3.82 (d, J=11.33 Hz, 1 H), 3.89 (d, J=8.40 Hz, 1 H), 3.97 (m, 2 H), 4.51 (d, J=7.62 Hz, 2 H), 7.99 (m, 2 H), 8.19 (s, 1 H); MS (ESI) (M+H)⁺ 400.2; Anal. Calcd for C₂₃H₃₃N₃O₃ + 1.5 TFA + 0.7 H₂O: C, 53.55; H, 6.20; N, 7.21. Found: C, 53.51; H, 6.21; N, 7.29.

Example 19

(4S)-2-[[1-(Cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1H-benzimidazol-5-yl]carbonyl]isoxazolidin-4-ol

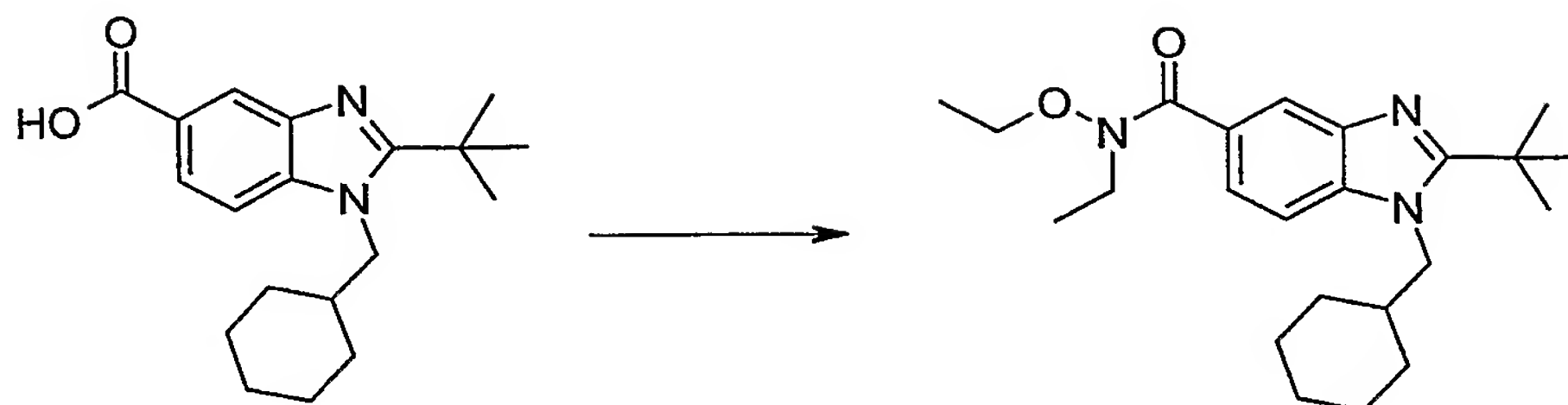


Following the same procedure in Example 4, Step A, using 1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1H-benzimidazole-5-carboxylic acid (50 mg, 0.152 mmol) (for preparation, see Steps B, C, D and E in Example 4) (4S)-isoxazolidin-4-ol hydrochloride (21 mg, 0.167 mmol), HATU (69 mg, 0.182 mmol) and diisopropylethylamine (0.066 mL, 0.380 mmol) in 2 mL of DMF. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O on a C-18 column and then lyophilized affording the desired title compound as the corresponding TFA salt. Yield: 74 mg (95%). ¹H NMR (400 MHz, METHANOL-D₄): δ 0.86 (t, J=7.52 Hz, 3 H), 1.26 (m, 5 H), 1.65 (m, 2 H), 1.69 (s, 7 H), 1.79 (m, 2 H), 2.04 (q, J=7.42 Hz, 2 H), 2.13 (m, 1 H), 3.84 (d, J=11.91 Hz, 1 H), 4.00 (d, J=8.01 Hz, 1 H), 4.07 (m, 2 H), 4.51 (d, J=7.62 Hz, 2 H), 4.82 (m, 1 H), 8.00 (m, 2 H), 8.20 (m, 1 H); MS (ESI) (M+H)⁺ 400.2; Anal. Calcd for C₂₃H₃₃N₃O₃ + 1.7 TFA + 1.5 H₂O: C, 51.11; H, 6.13; N, 6.77. Found: C, 51.12; H, 6.00; N, 7.03.

Example 20

2-tert-Butyl-1-(cyclohexylmethyl)-N-ethoxy-N-ethyl-1H-benzimidazole-5-carboxamide

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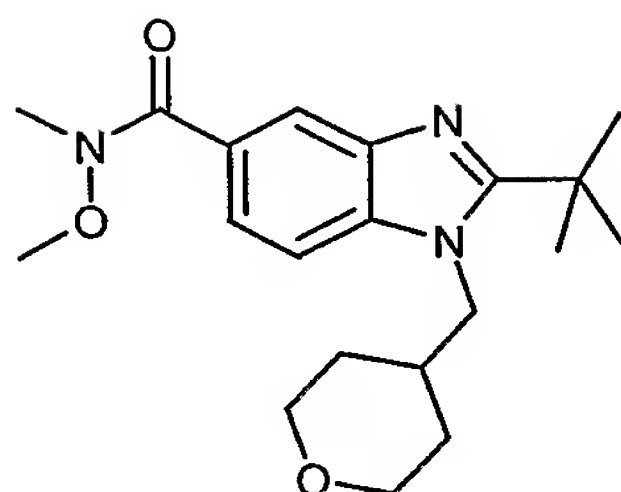


2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazole-5-carboxylic acid (lithium salt) (100 mg, 0.312 mmol) (for preparation, see example 3, Steps B to F), O-ethylhydroxylamine hydrochloride (36 mg, 0.374 mmol), HATU (140 mg, 0.374 mmol) and diisopropylethylamine (0.135 mL, 0.780 mmol) were stirred in 3 mL of DMF at RT for 2h. The solvent was concentrated. The residue was dissolved in EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. The crude product was dissolved in 4 mL of DMF and then added dropwise to a cold (0°C) stirring DMF solution (1 mL) of NaH (60% dispersion in oil) (15 mg, 0.374 mmol). Ethyl iodide (0.050 mL, 0.624 mmol) was then added and the solution was stirred at rt overnight. The reaction was quenched at 0°C by addition of saturated aqueous NH₄Cl solution and the solvent was concentrated. The residue was dissolved in EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O on a C-18 column and then lyophilized affording the desired title compound as the corresponding TFA salt. Yield: 68 mg (44%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.03 (t, J=7.03 Hz, 3 H), 1.27 (m, 5 H), 1.33 (t, J=7.13 Hz, 3 H), 1.66 (m, 2 H), 1.70 (s, 10 H), 1.79 (m, 2 H), 2.15 (m, 1 H), 3.84 (m, 4 H), 4.51 (d, J=7.62 Hz, 2 H), 7.88 (dd, J=8.79, 1.56 Hz, 1 H), 8.00 (dd, J=8.79, 0.59 Hz, 1 H), 8.06 (d, J=0.78 Hz, 1 H); MS (ESI) (M+H)⁺ 386.2; Anal. Calcd for C₂₃H₃₅N₃O₂ + 1.2 TFA + 0.7 H₂O: C, 57.03; H, 7.08; N, 7.85. Found: C, 56.99; H, 7.00; N, 7.80.

Example 21

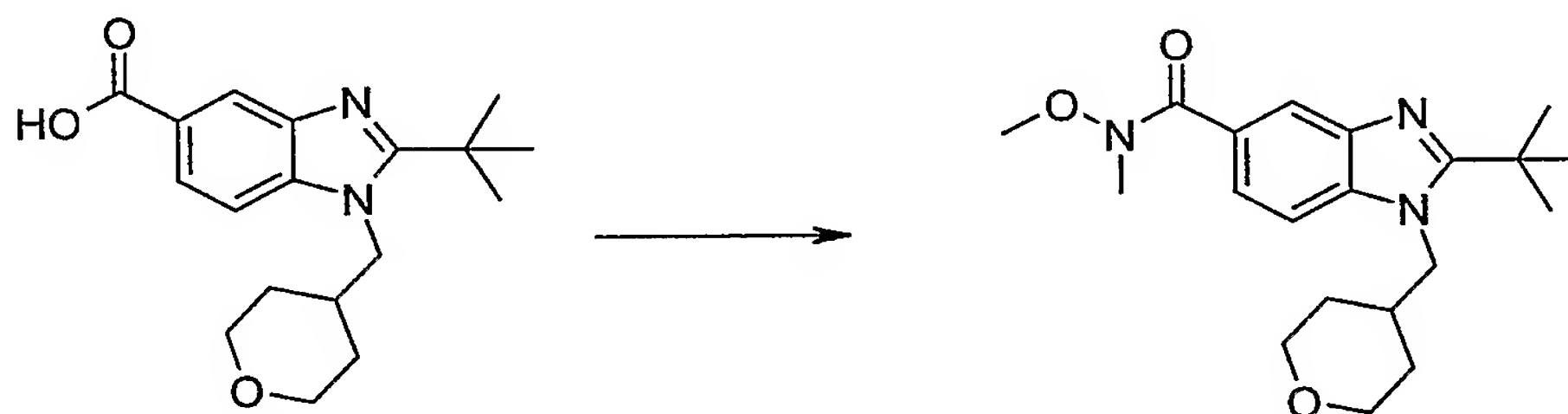
2-*tert*-Butyl-N-methoxy-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazole-5-carboxamide

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Step A: 2-*tert*-Butyl-N-methoxy-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole-5-carboxamide

5



2-*tert*-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole-5-carboxylic acid

(lithium salt) (for preparation refer to the following Steps B to E) (50 mg, 0.155 mmol), N,O-

10 dimethylhydroxylamine hydrochloride (17 mg, 0.171 mmol) and HATU (70 mg, 0.186 mmol)

were stirred in 3 mL of DMF containing diisopropylethylamine (0.040 mL, 0.233 mmol) at RT for 2h. The solvent was concentrated and the product was purified by reversed-phase

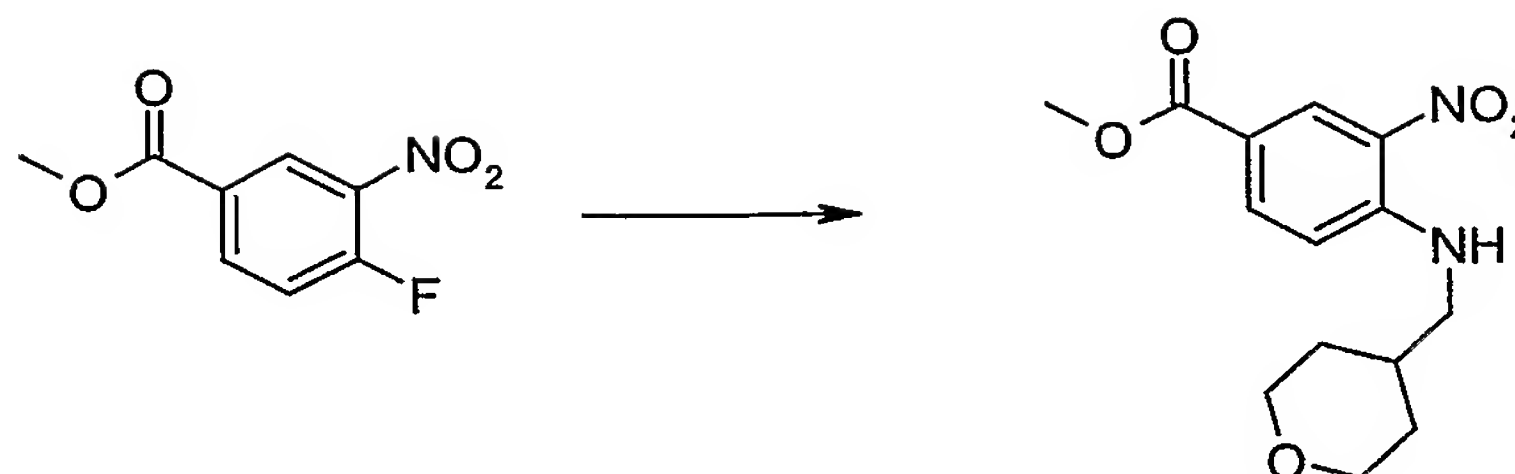
HPLC using 10-50% CH₃CN/H₂O on a C-18 column and then lyophilized affording the

desired title compound as the corresponding TFA salt. Yield: 55 mg (75%). ¹H NMR (400

15 MHz, METHANOL-D₄): δ 1.55 (m, 3 H), 1.61 (m, 1 H), 1.69 (s, 9 H), 2.40 (m, 1 H), 3.35 (m, 2 H), 3.40 (s, 3 H), 3.57 (s, 3 H), 3.92 (d, J=3.12 Hz, 1 H), 3.95 (m, 1 H), 4.56 (dd, J=7.42 Hz, 2 H), 7.88 (dd, J=8.79, 1.37 Hz, 1 H), 8.01 (d, J=8.79 Hz, 1 H), 8.07 (m, J=1.37 Hz, 1 H); MS (ESI) (M+H)⁺ 360.3; Anal. Calcd for C₂₀H₂₉N₃O₃ + 1.6 TFA + 1.1 H₂O: C, 49.61; H, 5.89; N, 7.48. Found: C, 49.63; H, 5.89; N, 7.53.

20 **Step B: Methyl 3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]benzoate**

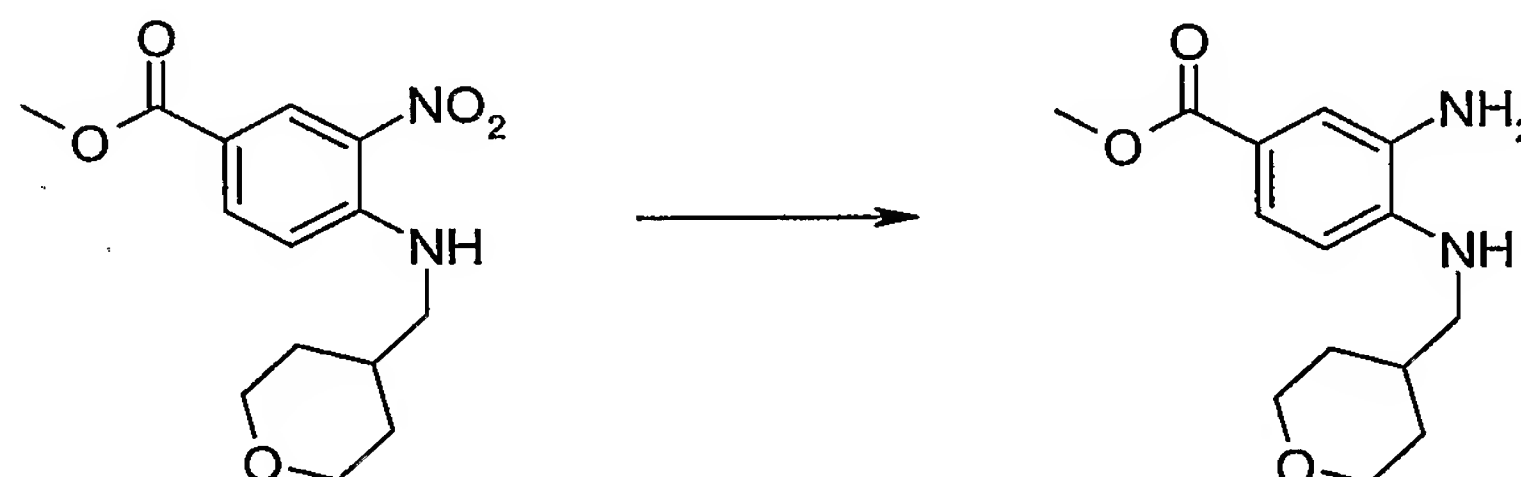
- 46 -



Methyl 4-fluoro-3-nitrobenzoate (400 mg, 2.01 mmol) (for preparation, see example 3, Step B) and 4-aminomethyltetrahydropyran (280 mg, 2.41 mmol) were stirred in 5 mL of EtOH containing triethylamine (0.420 mL, 3.02 mmol) at 75°C for 4h. The solvent was concentrated. The residue was dissolved in EtOAc and washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 2:1 / hexanes:EtOAc as eluent on silica gel to produce the desired title compound. Yield: 545 mg (92%). ¹H NMR (400 MHz, CHLOROFORM-D):

δ 1.39-1.51 (m, 2 H), 1.74 (d, J=1.76 Hz, 1 H), 1.78 (d, J=1.95 Hz, 1 H), 1.93 - 2.03 (m, 1 H), 3.28 (dd, J=6.83, 5.66 Hz, 2 H), 3.43 (td, J=11.86, 2.05 Hz, 2 H), 3.91 (s, 3 H), 4.02 (d, J=3.91 Hz, 1 H), 4.05 (d, J=3.91 Hz, 1 H), 6.87 (d, J=8.98 Hz, 1 H), 8.06 (ddd, J=9.08, 2.05, 0.78 Hz, 1 H), 8.42-8.49 (m, 1 H), 8.89 (d, J=2.15 Hz, 1 H).

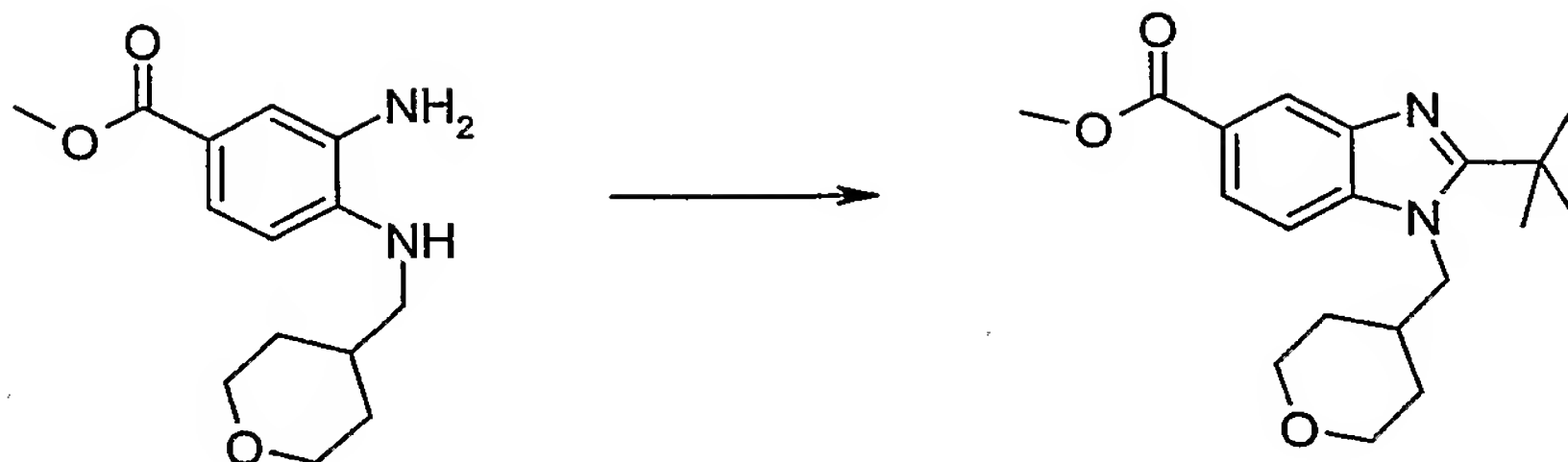
Step C: Methyl 3-amino-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]benzoate



Methyl 3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]benzoate (540 mg, 1.83 mmol) was dissolved in 50 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken in a Parr hydrogenation apparatus under H₂ atmosphere (45 psi) at RT for 6h. The solution was filtered through celite and the solvent was concentrated. Yield: 455 mg (94%); MS (ESI) (M+H)⁺ 264.93.

Step D: Methyl 2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole-5-carboxylate

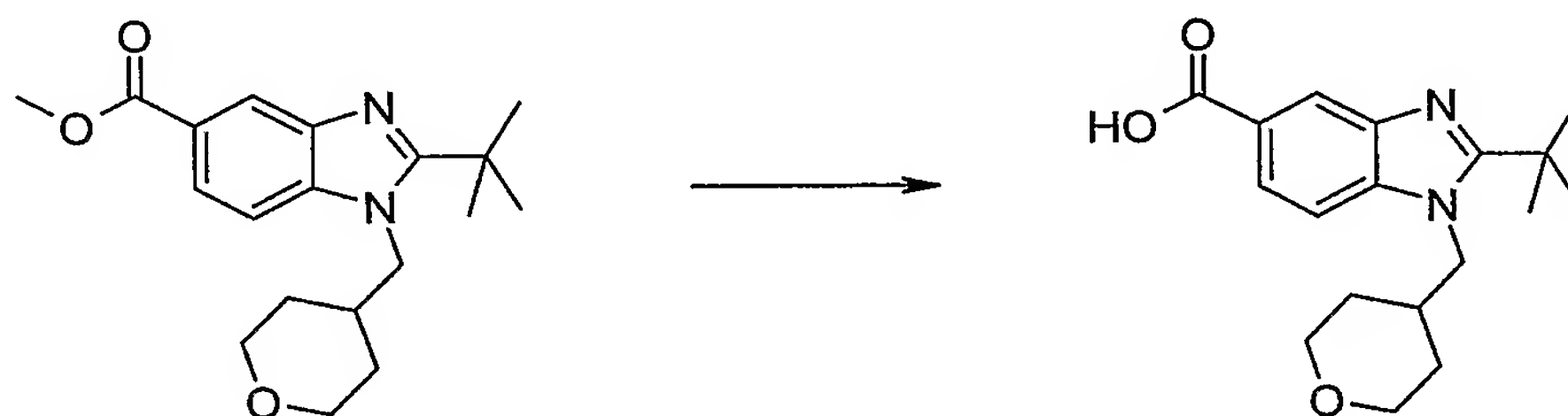
- 47 -



Methyl 3-amino-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]benzoate (455 mg, 1.72 mmol) and a catalytic amount of DMAP were dissolved in 25 mL of DCM. Trimethylacetyl chloride (0.230 mL, 1.89 mmol) was added dropwise and the solution was stirred at RT for 2h. The solution was washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. The residue was divided in three portions and each sample was dissolved in 4 mL of glacial acetic acid in a sealed tube. Each solution was heated at 175°C in a Smithsynthesizer (Personal Chemistry) microwave instrument for 1h.

The samples were pooled together and the solvent was concentrated. The residue was dissolved in EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 2:1 / hexanes:acetone as eluent on silica gel to produce the desired title compound. Yield: 237 mg (42%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.51 (m, 3 H), 1.55 (m, 1 H), 1.58 (s, 9 H), 2.29 (m, 1 H), 3.31 (m, 2 H), 3.93 (s, 3 H), 3.96 (m, 1 H), 3.99 (t, J=3.03 Hz, 1 H), 4.23 (d, J=7.42 Hz, 2 H), 7.35 (d, J=8.59 Hz, 1 H), 7.96 (dd, J=8.59, 1.56 Hz, 1 H), 8.47 (d, J=0.98 Hz, 1 H).

Step E: 2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole-5-carboxylic acid



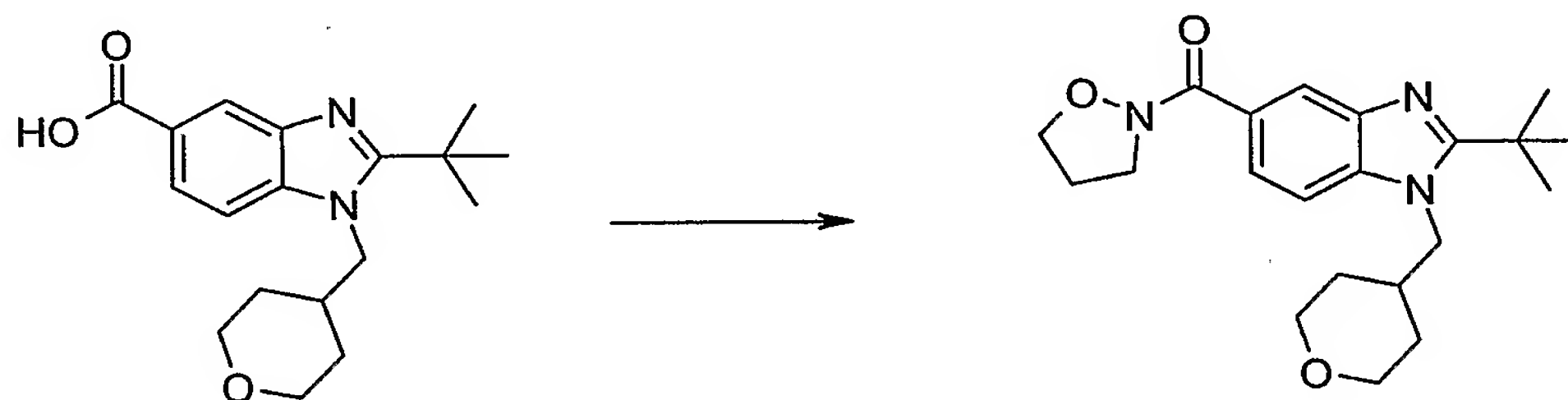
Methyl 2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole-5-carboxylate (230mg, 0.696 mmol) was dissolved in 5 mL of EtOH. 1M LiOH (0.765 mL, 0.766 mmol) was added and the solution was refluxed for 3h. The solvent was concentrated and the

- 48 -

product was isolated as the lithium salt and used directly for the next step. Yield: 240 mg (99%). MS (ESI) (M+H)⁺ 317.23.

Example 22

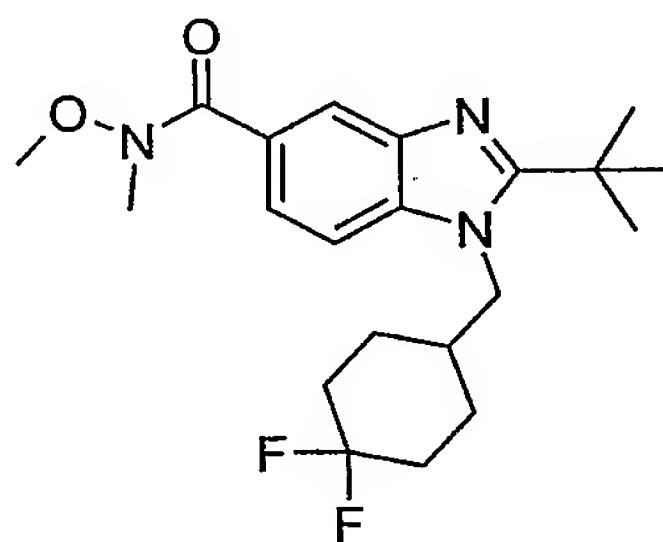
2-tert-Butyl-5-(isoxazolidin-2-ylcarbonyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole



Following the same procedure in Example 3, Step A, using 2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole-5-carboxylic acid (lithium salt) (50 mg, 0.156 mmol), isoxazolidine hydrochloride (19 mg, 0.172 mmol), HATU (70 mg, 0.187 mmol) and diisopropylethylamine (0.040 mL, 0.233 mmol) in 3 mL of DMF. The product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O on a C-18 column and then lyophilized affording the desired title compound as the corresponding TFA salt. Yield: 57 mg (76%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.55 (m, 3 H), 1.60 (m, 1 H), 1.69 (s, 9 H), 2.40 (m, 3 H), 3.34 (dt, J=11.67, 2.44 Hz, 2 H), 3.93 (m, 4 H), 4.05 (t, J=6.74 Hz, 2 H), 4.55 (d, J=7.42 Hz, 2 H), 7.98 (m, 2 H), 8.17 (m, 1 H); MS (ESI) (M+H)⁺ 372.3; Anal. Calcd for C₂₁H₂₉N₃O₃ + 1.4 TFA + 0.8 H₂O: C, 52.40; H, 5.91; N, 7.70. Found: C, 52.37; H, 5.97; N, 7.65.

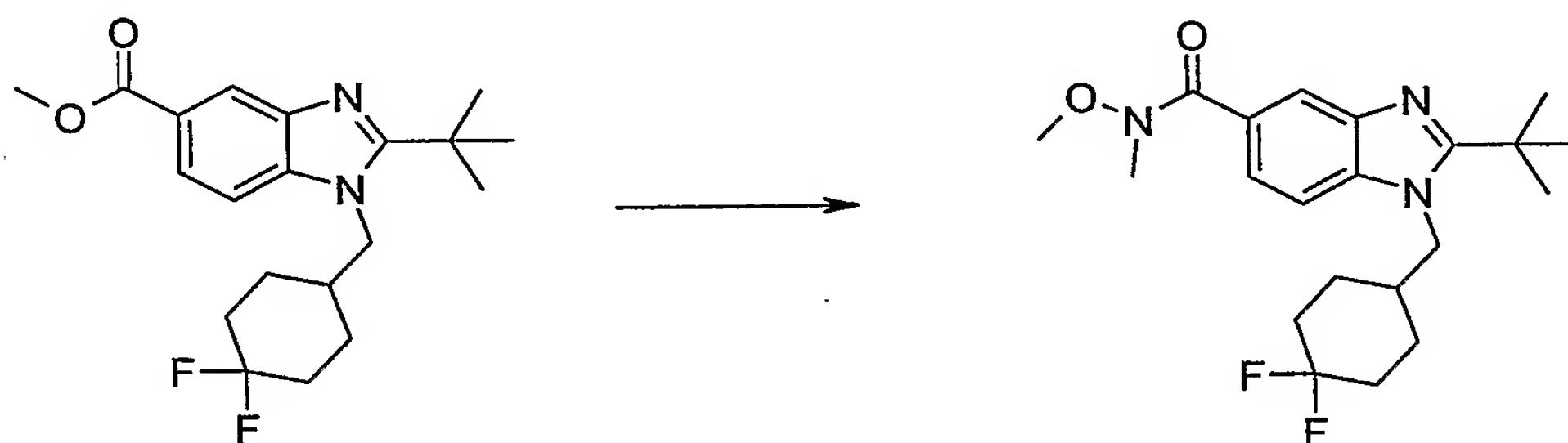
Example 23

2-tert-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-N-methoxy-N-methyl-1H-benzimidazole-5-carboxamide



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Step A: 2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-N-methoxy-N-methyl-1H-benzimidazole-5-carboxamide



5

Methyl 2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1H-benzimidazole-5-carboxylate (33mg, 0.0905 mmol) (for preparation see following Steps B to F) was refluxed in a 1:1 mixture of EtOH:H₂O containing 1M LiOH (0.100 mL, 0.0996 mmol) for 3h. The solvent was evaporated. The residue was then dissolved in 5 mL of DMF and HATU (41 mg, 0.0996

10

mmol), N,O-dimethylhydroxylamine hydrochloride (11 mg, 0.109 mmol) and diisopropylethylamine (0.024 mL, 0.149 mmol) were added. The solution was stirred at RT for 1h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was

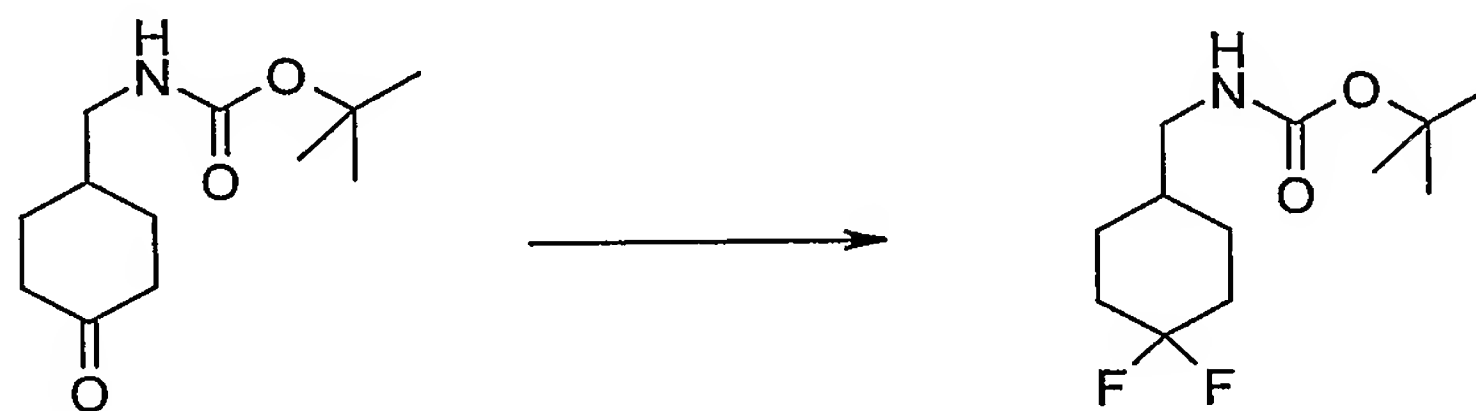
15

lyophilized affording the desired title compound as the corresponding TFA salt. Yield: 32 mg (70%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.54 - 1.65 (m, 2 H), 1.70 (s, 9 H), 1.74 - 1.84 (m, 4 H), 2.03 - 2.12 (m, 2 H), 2.24 - 2.34 (m, 1 H), 3.41 (s, 3 H), 3.58 (s, 3 H), 4.59 (d, J=7.42 Hz, 2 H), 7.90 (dd, J=8.79, 1.37 Hz, 1 H), 8.02 (d, J=8.79 Hz, 1 H), 8.08 (s, 1 H); MS (ESI) (M+H)⁺ 394.2; Anal. Calcd for C₂₁H₂₉N₃O₂F₂ + 1.2 TFA + 0.7 H₂O: C, 51.77; H, 5.87;

20

N, 7.74. Found: C, 51.72; H, 5.63; N, 8.14.

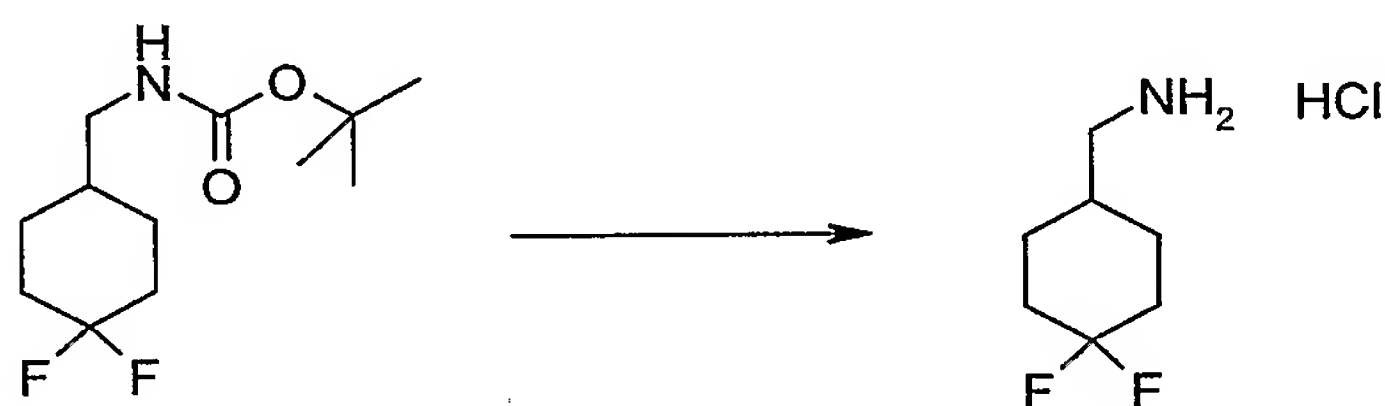
Step B: *tert*-Butyl [(4,4-difluorocyclohexyl)methyl]carbamate



- 50 -

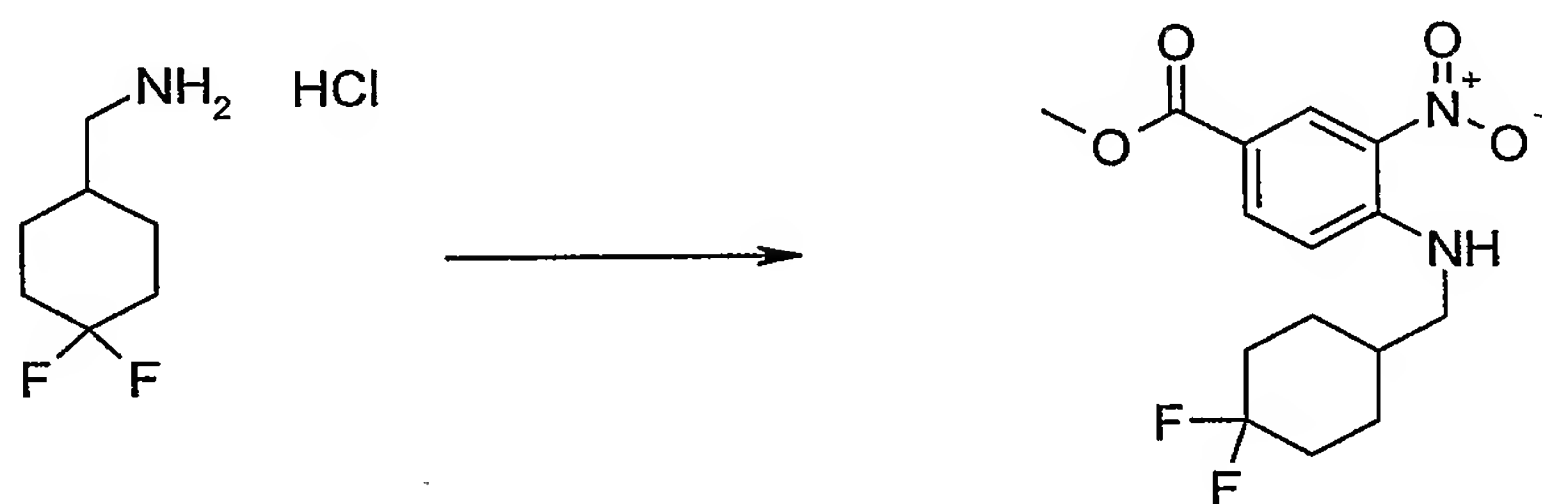
4-N-Boc-aminomethyl cyclohexanone (500 mg, 2.2 mmol) was dissolved in 20 mL of DCM at 0°C under nitrogen. DAST (0.580 mL, 4.4 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 3:1 / hexanes:EtOAc as eluent on silica gel to produce the desired title compound. Yield: 221 mg (40%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.28 (m, 2 H), 1.44 (s, 9 H), 1.54 (m, 1 H), 1.68 (m, 1 H), 1.77 (m, 3 H), 2.09 (m, 2 H), 3.03 (t, J=6.54 Hz, 2 H), 4.62 (m, 1 H).

Step C: [(4,4-Difluorocyclohexyl)methyl]amine hydrochloride



tert-Butyl [(4,4-difluorocyclohexyl)methyl]carbamate (215mg, 0.862 mmol) was stirred in 3 mL of 1M HCl/AcOH at RT for 1h. The solvent was concentrated and the residue was washed with ether and dried under vacuum. Yield: 135 mg (85%); ¹H NMR (400 MHz, METHANOL-D₄): δ 1.34 (m, 2 H), 1.76 (m, 2 H), 1.85 (m, 2 H), 1.88 (m, 2 H), 2.09 (m, 2 H), 2.86 (d, J=7.03 Hz, 2 H).

Step D: Methyl 4-[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrobenzoate



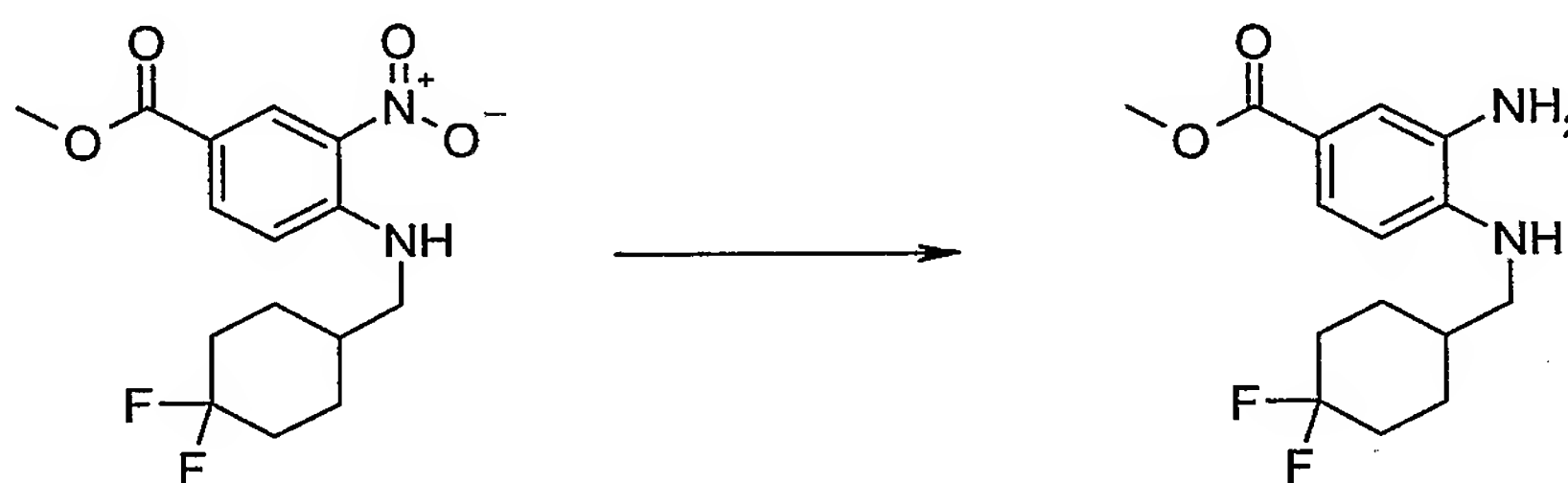
Methyl 4-fluoro-3-nitrobenzoate (50 mg, 0.251 mmol) (for preparation, see example 3, Step B) and [(4,4-difluorocyclohexyl)methyl]amine hydrochloride (55 mg, 0.301 mmol) were stirred in 3 mL of EtOH containing triethylamine (0.052 mL, 0.376 mmol) at 75°C for 4h.

The solvent was concentrated. The residue was dissolved in EtOAc and washed with 5%

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KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 4:1 / hexanes:EtOAc as eluent on silica gel to produce the desired title compound. Yield: 84 mg (99%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.43 (ddd, J=12.99, 12.64, 3.51 Hz, 2H), 1.67–1.75 (m, 1 H), 1.75–1.86 (m, 2 H), 1.91–1.95 (m, 1 H), 1.95–1.99 (m, 1 H), 2.12–2.22 (m, 2 H), 3.29 (dd, J=6.83, 5.66 Hz, 2 H), 3.91 (s, 3 H), 6.86 (d, J=8.98 Hz, 1 H), 8.07 (ddd, J=9.03, 2.00, 0.68 Hz, 1 H), 8.42–8.51 (m, 1 H), 8.90 (d, J=2.15 Hz, 1 H).

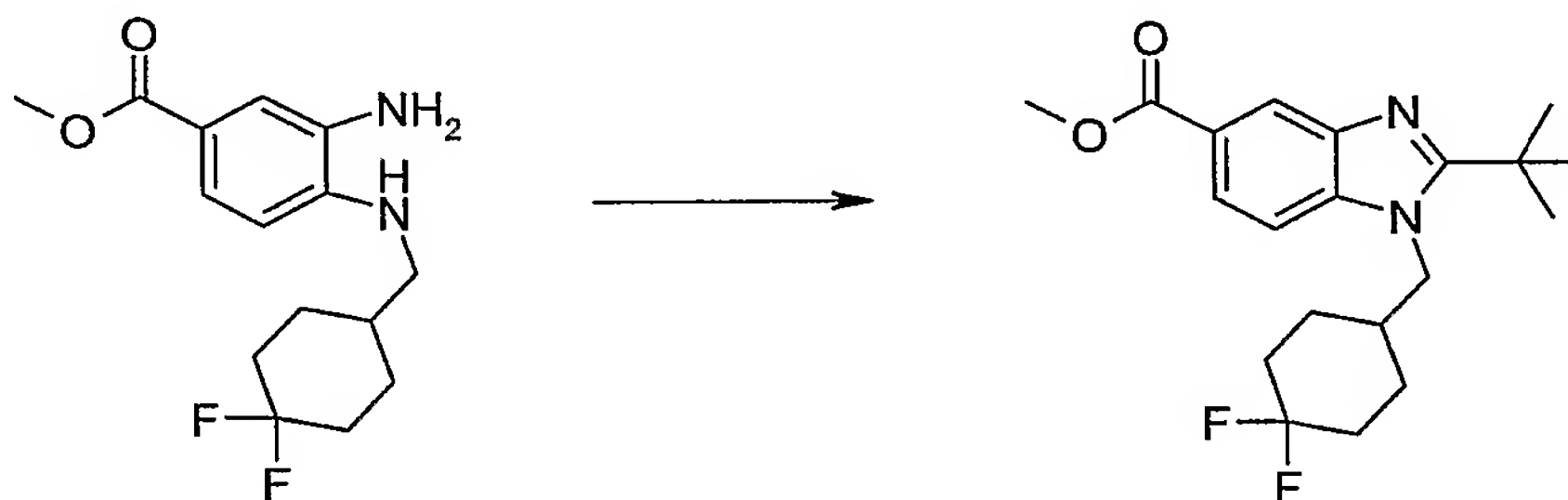
Step E: Methyl 3-amino-4-[[[(4,4-difluorocyclohexyl)methyl]amino]benzoate



Methyl 4-[[[(4,4-difluorocyclohexyl)methyl]amino]-3-nitrobenzoate (80 mg, 0.244 mmol) was dissolved in 20 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken in a Parr hydrogenation apparatus under H₂ atmosphere (45 psi) at RT for 5h.

The solution was filtered through celite and the solvent was concentrated. Yield: 73 mg (99%); MS (ESI) (M+H)⁺ 299.21.

Step F: Methyl 2-*tert*-butyl-1-[[[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazole-5-carboxylate



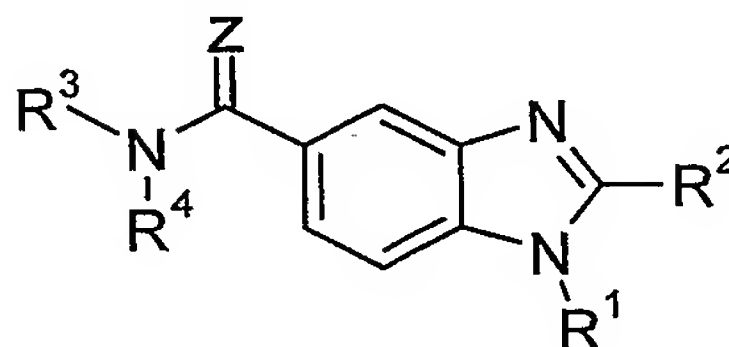
Methyl 3-amino-4-[[[(4,4-difluorocyclohexyl)methyl]amino]benzoate (70 mg, 0.235 mmol) and DMAP (5 mg, 0.047 mmol) were dissolved in 5 mL of DCM. Trimethylacetyl chloride (0.031 mL, 0.259 mmol) was added dropwise and the solution was stirred at RT for 3h. The

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solution was washed with saturated NaHCO_3 solution, brine and dried over anhydrous MgSO_4 . The solvent was evaporated. The residue was divided dissolved in 3 mL of glacial acetic acid in a sealed tube. The solution was heated at 175°C in a Smithsynthesizer (Personal Chemistry) microwave instrument for 4 X 1h. The solvent was concentrated. The
5 residue was dissolved in EtOAc and washed with saturated NaHCO_3 solution, brine and dried over anhydrous MgSO_4 . The crude product was purified by flash chromatography using 2:1 / hexanes:EtOAc as eluent on silica gel to produce the desired title compound. Yield: 33 mg (39%). ^1H NMR (400 MHz, CHCl_3 - d_3): δ 1.44 – 1.54 (m, 2 H), 1.56 (s, 9 H), 1.59–1.67 (m, 1 H), 1.66–1.73 (m, 3 H), 2.07–2.18 (m, 3 H), 3.92 (s, 3 H), 4.23 (d, $J=7.42$ Hz, 2 H),
10 7.31 (d, $J=8.59$ Hz, 1 H), 7.95 (dd, $J=8.59, 1.56$ Hz, 1 H), 8.48 (s, 1 H).

What is claimed is:

1. A compound of formula I or a pharmaceutically acceptable salt thereof:



I

wherein

Z is selected from O= and S=;

R¹ is selected from C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, R⁵R⁶N-C₁₋₆alkyl, R⁵O-C₁₋₆alkyl, R⁵C(=O)N(-R⁶)-C₁₋₆alkyl, R⁵R⁶NS(=O)₂-C₁₋₆alkyl, R⁵CS(=O)₂N(-R⁶)-C₁₋₆alkyl, R⁵R⁶NC(=O)N(-R⁷)-C₁₋₆alkyl, R⁵R⁶NS(=O)₂N(R⁷)-C₁₋₆alkyl, C₆₋₁₀aryl-C₁₋₆alkyl, C₆₋₁₀aryl-C(=O)-C₁₋₆alkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocyclyl-C₁₋₆alkyl, C₃₋₆heterocyclyl-C(=O)-C₁₋₆alkyl, C₁₋₁₀hydrocarbylamino, R⁵R⁶N-, R⁵O-, R⁵C(=O)N(-R⁶)-, R⁵R⁶NS(=O)₂-, R⁵CS(=O)₂N(-R⁶)-, R⁵R⁶NC(=O)N(-R⁷)-, R⁵R⁶NS(=O)₂N(R⁷)-, C₆₋₁₀aryl, C₆₋₁₀aryl-C(=O)-, C₃₋₁₀cycloalkyl, C₄₋₈cycloalkenyl, C₃₋₆heterocyclyl and C₃₋₆heterocyclyl-C(=O)-; wherein said C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₆₋₁₀aryl-C₁₋₆alkyl, C₆₋₁₀aryl-C(=O)-C₁₋₆alkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocyclyl-C₁₋₆alkyl, C₃₋₆heterocyclyl-C(=O)-C₁₋₆alkyl, C₁₋₁₀hydrocarbylamino, C₆₋₁₀aryl, C₆₋₁₀aryl-C(=O)-, C₃₋₁₀cycloalkyl, C₄₋₈cycloalkenyl, C₃₋₆heterocyclyl or C₃₋₆heterocyclyl-C(=O)- used in defining R¹ is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and -NR⁵R⁶;

R² is selected from the group consisting of C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl, R⁵R⁶N-, C₃₋₅heteroaryl, C₆₋₁₀aryl and C₃₋₆heterocycloalkyl, wherein said C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl, C₃₋₅heteroaryl, C₆₋₁₀aryl or C₃₋₆heterocycloalkyl used in defining R² is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and -NR⁵R⁶;

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wherein R^5 , R^6 and R^7 are independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a divalent C_{1-6} group that together with another divalent R^5 , R^6 or R^7 forms a portion of a ring; and

R^3 and R^4 are independently selected from $-H$, $-OH$, amino, R^8 and $-O-R^8$, wherein R^8 is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a divalent C_{1-6} group that together with another divalent R^8 forms a portion of a ring, wherein R^3 and R^4 are not $-H$ at the same time, and wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or divalent C_{1-6} group in defining R^8 is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, hydroxy, carboxy and $-NR^5R^6$; or R^3 and R^4 together with the nitrogen connected thereto form a portion of a 5- or 6-membered ring, wherein said ring is optionally substituted by one or more groupd selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, hydroxy, carboxy and $-NR^5R^6$.

2. A compound as claimed in claim 1, wherein

15 Z is $O=$;

R^1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $R^5R^6N-C_{1-4}$ alkyl, R^5O-C_{1-4} alkyl, $R^5C(=O)N(-R^6)-C_{1-4}$ alkyl, phenyl- C_{1-4} alkyl, phenyl- $C(=O)-C_{1-4}$ alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-4}$ alkyl, R^5R^6N- , R^5O- , $R^5R^6NS(=O)_2-$, C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-6} cycloalkenyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- $C(=O)-$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl- C_{1-4} alkyl, phenyl- $C(=O)-C_{1-4}$ alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-4}$ alkyl, C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-6} cycloalkenyl, C_{3-6} heterocyclyl or C_{3-6} heterocyclyl- $C(=O)-$ used in defining R^1 is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and R^5R^6N- ;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl, C_{3-5} heteroaryl, R^5R^6N- , phenyl and C_{3-6} heterocycloalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl, C_{3-5} heteroaryl, phenyl or C_{3-6} heterocycloalkyl used in defining R^2 is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and R^5R^6N- ;

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R^3 and R^4 are independently selected from $-OH$, amino, C_{1-6} alkyl and C_{1-6} alkoxy, or R^3 and R^4 together with the nitrogen connected thereto form a portion of a 5- or 6-membered ring, wherein said ring is optionally substituted by a group selected from hydroxy, carboxy, methyl and ethyl; and

5 R^5 and R^6 are independently selected from $-H$, C_{1-6} alkyl and C_{2-6} alkenyl.

3. A compound as claimed claim 1, wherein

Z is $O=$;

R^1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, $R^5R^6N-C_{1-4}$ alkyl, R^5O-C_{1-4} alkyl,
 10 $R^5C(=O)N(-R^6)-C_{1-4}$ alkyl, phenyl- C_{1-4} alkyl, phenyl- $C(=O)-C_{1-4}$ alkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-4}$ alkyl, phenyl, C_{3-6} cycloalkyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- $C(=O)-$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, $R^5R^6N-C_{1-4}$ alkyl, R^5O-C_{1-4} alkyl, $R^5C(=O)N(-R^6)-C_{1-4}$ alkyl, phenyl- C_{1-4} alkyl, phenyl- $C(=O)-C_{1-4}$ alkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-4}$ alkyl, phenyl, C_{3-6} cycloalkyl, C_{3-6} heterocyclyl or C_{3-6} heterocyclyl- $C(=O)-$ used in defining R^1 is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and R^5R^6N- ;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, R^5R^6N- ,
 20 C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl, C_{3-5} heteroaryl, and phenyl wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl, C_{3-5} heteroaryl, and phenyl used in defining R^2 is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and R^5R^6N- ;

25 R^5 and R^6 are independently selected from $-H$, C_{1-6} alkyl and C_{2-6} alkenyl; and

R^3 and R^4 are independently selected from $-OH$, amino, C_{1-6} alkyl and C_{1-6} alkoxy; or R^3 and R^4 together with the nitrogen connected thereto form a portion of a 5- or 6-membered ring wherein said ring is optionally substituted by a group selected from hydroxy, methoxy, ethoxy, methyl and ethyl.

30

4. A compound as claimed in claim 1, wherein

Z is $O=$;

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R¹ is selected from cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl, ethyl, propyl, adamantyl, adamantylmethyl, allyl, isopentyl, benzyl, methoxyethyl, tetrahydropyranylmethyl, tetrahydrofuranylmethyl, cyclohexyloxy, cyclohexylamino, dimethylaminoethyl, 4-pyridylmethyl, 2-pyridylmethyl, 1-pyrrolylethyl, 1-morpholinoethyl, 4,4-difluoro-cyclohexylmethyl, cyclohexylmethyl, 2-pyrrolidylmethyl, N-methyl-2-pyrrolidylmethyl, 2-piperidylmethyl, N-methyl-2-piperidylmethyl, 3-thienylmethyl, (2-nitrothiophene-5-yl)-methyl, (1-methyl-1H-imidazole-2-yl)methyl, (5-(acetoxymethyl)-2-furyl)methyl, (2,3-dihydro-1H-isoindole-1-yl)methyl, and 5-(2-methylthiazolyl);

R² is selected from t-butyl, n-butyl, 2-methyl-2-butyl, cyclohexyl, cyclohexylmethyl, n-pentyl, isopentyl, trifluoromethyl, 1,1-difluoroethyl, N-piperidyl, dimethylamino, phenyl, pyridyl, tetrahydrofuranyl, tetrahydropyranyl, 2-methoxy-2-propyl, and N-morpholinyl; and

R³ and R⁴ are independently selected from methyl, ethyl, hydroxy, methoxy and ethoxy; or R³ and R⁴ together with the nitrogen connected thereto form a group selected from isoxazolidin-2-yl, 4-hydroxy-isoxazolidin-2-yl, 4-hydroxy-4-methyl-isoxazolidin-2-yl, N-morpholinyl.

5. A compound selected from:

2-*tert*-Butyl-*N,N*-diethyl-1-{[(2*R*)-1-methylpiperidin-2-yl]methyl}-1*H*-benzimidazole-5-carboxamide,

2-*tert*-Butyl-1-(cyclohexylmethyl)-*N,N*-diethyl-1*H*-benzimidazole-5-carboxamide,
2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methoxy-*N*-methyl-1*H*-benzimidazole-5-carboxamide,

1-(Cyclohexylmethyl)-2-(1,1-dimethylpropyl)-*N*-methoxy-*N*-methyl-1*H*-benzimidazole-5-carboxamide,

1-(Cyclohexylmethyl)-2-(1,1-dimethylpropyl)-*N*-methoxy-*N*-methyl-1*H*-benzimidazole-5-carboxamide ,

1-(Cyclohexylmethyl)-2-(1,1-dimethylpropyl)-*N*-morpholin-4-yl-1*H*-benzimidazole-5-carboxamide,

1-(Cyclohexylmethyl)-2-(1,1-dimethylpropyl)-5-(morpholin-4-ylcarbonyl)-1*H*-benzimidazole,

1-(Cyclohexylmethyl)-5-[(2,6-dimethylmorpholin-4-yl)carbonyl]-2-(1,1-dimethylpropyl)-1*H*-benzimidazole,

1-(Cyclohexylmethyl)-5-{[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]carbonyl}-2-(1,1-dimethylpropyl)-1*H*-benzimidazole,

1-(Cyclohexylmethyl)-2-(1,1-dimethylpropyl)-5-(isoxazolidin-2-ylcarbonyl)-1*H*-benzimidazole,

5 (4*R*)-2-{[1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazol-5-yl]carbonyl}-4-methylisoxazolidin-4-ol,

(4*S*)-2-{[1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazol-5-yl]carbonyl}-4-methylisoxazolidin-4-ol,

2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methoxy-1*H*-benzimidazole-5-carboxamide,

10 2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-ethoxy-1*H*-benzimidazole-5-carboxamide,

2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-ethyl-*N*-methyl-1*H*-benzimidazole-5-carboxamide,

(4*R*)-2-{[2-*Tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbonyl}isoxazolidin-4-ol,

15 (4*S*)-2-{[2-*Tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbonyl}isoxazolidin-4-ol,

2-*tert*-Butyl-1-(cyclohexylmethyl)-5-(isoxazolidin-2-ylcarbonyl)-1*H*-benzimidazole,

(4*R*)-2-{[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbonyl}-4-methylisoxazolidin-4-ol,

20 (4*S*)-2-{[1-(Cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazol-5-yl]carbonyl}isoxazolidin-4-ol,

2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-ethoxy-*N*-ethyl-1*H*-benzimidazole-5-carboxamide,

25 2-*tert*-Butyl-*N*-methoxy-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole-5-carboxamide,

2-*tert*-Butyl-5-(isoxazolidin-2-ylcarbonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole,

2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methoxy-*N*-methyl-1*H*-benzimidazole-5-carboxamide, and pharmaceutically acceptable salts thereof.

30

6. A compound according to any one of claims 1-5 for use as a medicament.

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7. The use of a compound according to any one of claims 1-5 in the manufacture of a medicament for the therapy of pain.

8. The use of a compound according to any one of claims 1-5 in the manufacture of a medicament for the treatment of anxiety disorders.

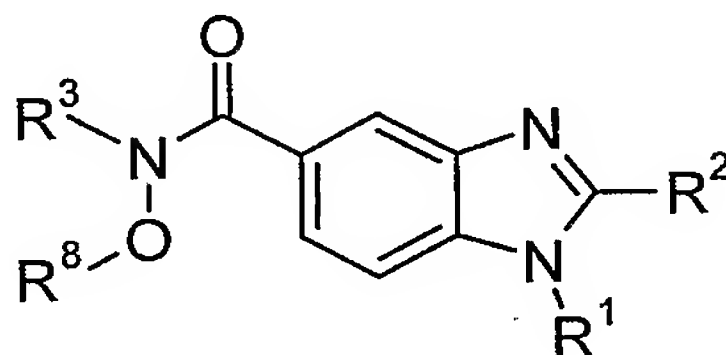
9. The use of a compound according to any one of claims 1-5 in the manufacture of a medicament for the treatment of cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, gastrointestinal disorders and cardiovascular disorders.

10

10. A pharmaceutical composition comprising a compound according to any one of claims 1-5 and a pharmaceutically acceptable carrier.

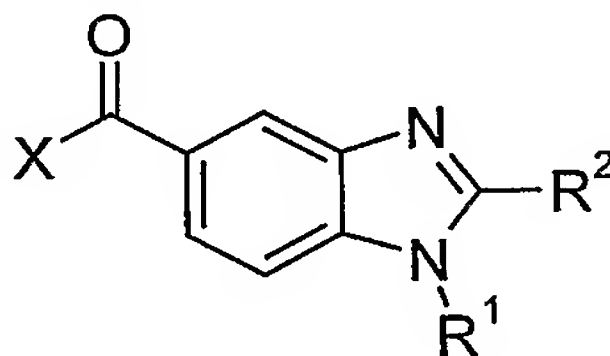
11. A method for the therapy of pain in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-5.

12. A method for preparing a compound of formula II,

II

20

comprising the step of reacting a compound of formula III,

III

25 with a compound of R^3NHOR^8 to form the compound of formula II, wherein

X is selected from Cl, Br, I and OH;

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- R^1 is selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $R^5R^6N-C_{1-6}$ alkyl, R^5O-C_{1-6} alkyl, $R^5C(=O)N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2-C_{1-6}$ alkyl, $R^5CS(=O)_2N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NC(=O)N(-R^7)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2N(R^7)-C_{1-6}$ alkyl, C_{6-10} aryl- C_{1-6} alkyl, C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-6}$ alkyl, C_{1-10} hydrocarbylamino, R^5R^6N- , R^5O- , $R^5C(=O)N(-R^6)-$, $R^5R^6NS(=O)_2-$, $R^5CS(=O)_2N(-R^6)-$, $R^5R^6NC(=O)N(-R^7)-$, $R^5R^6NS(=O)_2N(R^7)-$, C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-8} cycloalkenyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- $C(=O)-$; wherein said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{6-10} aryl- C_{1-6} alkyl, C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-6}$ alkyl, C_{1-10} hydrocarbylamino, C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-8} cycloalkenyl, C_{3-6} heterocyclyl or C_{3-6} heterocyclyl- $C(=O)-$ used in defining R^1 is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and $-NR^5R^6$;
- R^2 is selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl, R^5R^6N- , C_{3-5} heteroaryl, C_{6-10} aryl and C_{3-6} heterocycloalkyl, wherein said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl, C_{3-5} heteroaryl, C_{6-10} aryl or C_{3-6} heterocycloalkyl used in defining R^2 is optionally substituted by one or more groups selected from carboxy, halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and $-NR^5R^6$;

wherein R^5 , R^6 and R^7 are independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a divalent C_{1-6} group that together with another divalent R^5 , R^6 or R^7 forms a portion of a ring;

R^3 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a divalent C_{1-6} group that together with a divalent R^8 forms a portion of a ring; and

R^8 is selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a divalent C_{1-6} group that together with a divalent R^3 forms a portion of a ring.

INTERNATIONAL SEARCH REPORT

International Application No
GB2004/002427

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D235/08 C07D401/06 C07D405/06 A61K31/4184 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO 02/085866 A (WALPOLE CHRISTOPHER ; CHENG YUN-XING (CA); YANG HUA (CA); TOMASZEWSKI) 31 October 2002 (2002-10-31) the whole document | 1-12 |
| X | EP 0 882 718 A (FUJISAWA PHARMACEUTICAL CO) 9 December 1998 (1998-12-09) the whole document | 1-12 |
| X | GOEKER H ET AL: "SYNTHESIS OF SOME NEW BENZIMIDAZOLECARBOXAMIDES AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITY" FARMACO, SOCIETA CHIMICA ITALIANA, PAVIA, IT, vol. 53, no. 6, 1998, pages 415-420, XP000942653 ISSN: 0014-827X table 1 | 1-12 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|---|-----------------------|
| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | GOEKER H ET AL: "SYNTHESIS OF 1,2-DISUBSTITUTED BENZIMIDAZOLE-5(6)-CARBOXAMIDES AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITY" FARMACO, SOCIETA CHIMICA ITALIANA, PAVIA, IT, vol. 51, no. 1, 1996, pages 53-58, XP000942654 ISSN: 0014-827X table 1 ----- | 1-12 |
| X | H. GÖKER ET AL.: BIOORGANIC AND MEDICINAL CHEMISTRY, vol. 10, 2002, pages 2589-2596, XP002295583 examples 37,39; table 1 ----- | 1-12 |
| X | US 6 348 032 B1 (IXKES ULRICH ET AL) 19 February 2002 (2002-02-19) examples ----- | 1-12 |
| X | PATENT ABSTRACTS OF JAPAN vol. 0176, no. 74 (C-1140), 10 December 1993 (1993-12-10) & JP 5 222000 A (FUJISAWA PHARMACEUT CO LTD), 31 August 1993 (1993-08-31) * see RN 152712-72-6 * abstract ----- | 1-12 |
| X | PATENT ABSTRACTS OF JAPAN vol. 1996, no. 06, 28 June 1996 (1996-06-28) & JP 8 048671 A (KUREHA CHEM IND CO LTD), 20 February 1996 (1996-02-20) *see RN 176963-84-1 * abstract ----- | 1-12 |
| P,X | WO 03/053938 A (NOVO NORDISK AS) 3 July 2003 (2003-07-03) examples ----- | 1-12 |
| A | WO 03/027076 A (HERREMANS ARNOLDUS H J ; KRUSE CORNELIS G (NL); LANGE JOSEPHUS H M (NL) 3 April 2003 (2003-04-03) the whole document ----- | 1-12 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

/GB2004/002427

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|----|---------------------|--|--|
| WO 02085866 | A | 31-10-2002 | BR 0208907 A CA 2444381 A1 CZ 20032833 A3 EE 200300524 A EP 1390350 A1 HU 0303825 A2 NO 20034665 A WO 02085866 A1 US 2004116465 A1 | 20-04-2004 31-10-2002 12-05-2004 16-02-2004 25-02-2004 01-03-2004 10-12-2003 31-10-2002 17-06-2004 |
| EP 0882718 | A | 09-12-1998 | AU 722514 B2 AU 1209597 A BR 9612434 A EA 2357 B1 EP 0882718 A1 IL 124969 A JP 3063162 B2 NZ 324834 A US 6166219 A CA 2241186 A1 CN 1211238 A HU 9900625 A2 WO 9724334 A1 JP 2000159749 A TR 9801249 T2 US 6352985 B1 ZA 9610918 A AU 4400597 A WO 9815530 A1 TW 548272 B ZA 9708998 A | 03-08-2000 28-07-1997 28-12-1999 25-04-2002 09-12-1998 12-09-2002 12-07-2000 30-11-2001 26-12-2000 28-06-1997 17-03-1999 28-06-1999 10-07-1997 13-06-2000 21-10-1998 05-03-2002 08-07-1997 05-05-1998 16-04-1998 21-08-2003 20-04-1998 |
| US 6348032 | B1 | 19-02-2002 | US 2002082280 A1 | 27-06-2002 |
| JP 5222000 | A | 31-08-1993 | NONE | |
| JP 8048671 | A | 20-02-1996 | JP 3295277 B2 | 24-06-2002 |
| WO 03053938 | A | 03-07-2003 | WO 03047626 A1 WO 03053938 A1 EP 1453541 A1 US 2003138416 A1 US 2003212119 A1 | 12-06-2003 03-07-2003 08-09-2004 24-07-2003 13-11-2003 |
| WO 03027076 | A | 03-04-2003 | CA 2457444 A1 WO 03027076 A2 EP 1438296 A2 | 03-04-2003 03-04-2003 21-07-2004 |